PREVENTION OF STILLBIRTH IN Rh HÆMOLYTIC DISEASE

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IT is now established that most liveborn babies with hæmolytic disease of the newborn can be saved by exchange transfusion. Walker's (1958) analysis of 822 liveborn cases treated in the Newcastle hospitals between 1952 and 1957 gives a survival-rate of 97%. The stillbirth-rate reported in the same survey was 14·4%, and this demonstrates that the prevention of stillbirth is the outstanding problem in hæmolytic disease.

At present, premature delivery of the baby offers the only rational method of preventing stillbirth in this condition, but when the results of a clinical trial suggested that prematurity increased the risk of death from kernicterus in affected infants (Mollison and Walker 1952, Armitage and Mollison 1953), the practice of premature delivery in women found to have Rh antibodies was temporarily abandoned in many centres including the Bristol hospitals. The problem of kernicterus has been solved by the control of hyperbilirubinæmia by repeated exchange transfusion if necessary, and the claim by Kelsall and Vos (1952) that the severity of disease in the baby is closely related to the level of anti-Rh in the mother's serum determined by the indirect antiglobulin technique provided a criterion for selection of cases for premature delivery. By the middle of 1955 we considered that we had secured consistency in our indirect antiglobulin technique and that we were beginning to see a correlation between the titre of the mother's antibodies by this technique and the severity of hæmolytic disease in her baby. Since then we have become increasingly confident in predicting the severity, and consequently decide the management, of such cases from the results obtained by a carefully standardised titration technique, and we describe here an analysis of 262 consecutive affected babies born in the Bristol area since June, 1955. The series consists of 200 babies born to mothers who had not previously carried an affected child (first-affected babies) and 62 cases in which the mother had already had Rh antibodies during a previous pregnancy (subsequently-affected cases). These two groups are analysed separately.

First-affected Babies

The 200 babies analysed in table I were born during a three-and-a-half-year period. There is a close relationship between the titre of the mother's antibodies, determined by the indirect antiglobulin technique, and the risk of the pregnancy ending in stillbirth. The antibody levels are the maximum titres obtained during the antenatal period and were determined between the 34th and 36th weeks of the pregnancy.

Among 143 cases where the maternal antibody titre was below 1 in 40 there was only 1 stillbirth—a rate of 0·7%. In this series, therefore, the stillbirth-rate in a first-affected baby was 35 times greater (24·5%) when the mother's anti-Rh was at or above 1 in 40 than when the antenatal titre was below this titre. Striking although this difference is, it would almost certainly have been greater but for the fact that, during the latter part of the investigation, the obstetricians became more and more inclined to practise premature delivery when the mother's anti-Rh was found to have reached a titre of 1/40 or higher.

Including the neonatal deaths, the pregnancy ended in body titre was at or above 1/40, compared with approximately 1 in 30 cases at a titre of 1/10–1/20. There were no deaths in the 59 babies born to mothers with anti-Rh below a titre of 1/10. Deaths from all causes have been included in table I. None was the result of prematurity. In 3 of the babies a tentorial tear was almost certainly the cause of death rather than hæmolytic disease. Excluding these 3 cases from the analysis, 28% of the pregnancies ended in a dead baby when the mother's anti-Rh was 1/40 or above, and 1·4% when the titre was below 1/40.

In brief, therefore, as a result of this study we conclude that 1 in every 3 or 4 Rh negative mothers carrying a first-affected baby has a critically high titre of anti-Rh determined by the indirect antiglobulin technique, and that in such cases there is a risk of approximately 1 in 3

TABLE I—ANALYSIS OF 200 CONSECUTIVE FIRST-AFFECTED BABIES

—	Maternal indirect antiglobulin titre		
	<1/10	1/10–1/20	1/40 or higher
No. of cases	59	84	57
Stillbirth-rate (%)	0	1·2	24·5
Stillbirth or neonatal-death rate (%)	0	3·6	31·6
Need for transfusion (%)	15	71	98
Mild disease only (%)	85	29	2
Distribution (%)	29·5	42	28·5

or 4 that the pregnancy will end in a dead baby. By our technique, this titre is 1/40, and we are of the opinion that premature delivery should be considered when a mother has anti-Rh for the first time if the antibody titre has reached or exceeded 1/40.

This suggestion is supported by our finding that practically all babies (98%) born to mothers with antibodies at this titre required exchange transfusion, compared with 71% when the antibody titre was 1/10–1/20, and only 15% when the titre was below 1/10. The maternal titre of antibodies was not used as a criterion for deciding which infants required exchange transfusion. In agreement with generally accepted practice in England, the values of hæmoglobin and serum-bilirubin in the cord blood were the factors deciding which infants received an immediate exchange, while the subsequent development of dangerous levels of hyperbilirubinæmia made an exchange necessary in some infants which were not transfused immediately after birth.

Subsequently-affected Babies

During this investigation 62 babies were born to Rh-negative mothers who had previously carried a baby

TABLE II—ANALYSIS OF 62 CONSECUTIVE SUBSEQUENTLY-AFFECTED BABIES

	Maternal indirect antiglobulin titre		
	<1/10	1/10–1/20	1/40 or higher
No. of cases	7	32	23
Stillbirth-rate (%)	0	6·25	21·7
Sillbirth or neonatal-death rate (%)	0	9·4	34·8
Need for transfusion (%)	0	80	100
Mild disease only (%)	100	20	0
Distribution (%)	11	51·5	37·5

affected with hæmolytic disease. The outcome of these pregnancies in relationship to the maximum titres of the mother's anti-Rh during the antenatal period is analysed in table II.

Although the risk of stillbirth when the maternal titre of anti-Rh is 1/40 or higher is much the same as when the mother is carrying a first-affected baby, it is five times greater at the titre of 1/10–1/20. Kelsall et al. (1958) consider that not only the titre of the mother's antibodies, but also the time during which the baby's red blood-cells are exposed to this titre, is important in determining the severity of disease in the baby. Our finding that the risk of stillbirth is appreciably increased at this lower level of antibody titre supports this opinion. In most of these cases the baby would have been exposed to anti-Rh at a titre of 1/10–1/20 throughout almost the entire pregnancy, by contrast with a first-affected baby, when the mother's antibodies often do not attain this titre until the last weeks of the pregnancy.

The number of stillbirths when the mother's titre was 1/40 or higher would certainly have been greater but for the fact that practically all mothers who had previously carried a severely affected or stillborn baby were delivered prematurely. As table I shows, such mothers would usually have had a titre of at least 1/40 during the previous pregnancy, so that most of the premature deliveries in this group, although made primarily because of the history, were, in fact, in mothers with a titre of anti-Rh of 1/40 or more.

In 7 (approximately 11%) of the mothers the antenatal titre of anti-Rh did not rise as high as 1/10, even though the mother had had anti-Rh at a previous pregnancy. In all cases the baby proved to be only mildly affected and did not require treatment. This suggests that there may be a threshold for Rh antibodies, below which the baby will not suffer severe disease even when exposed to anti-Rh throughout the pregnancy. It offers an explanation for those puzzling cases in which the severity of the disease does not increase at all at each succeeding pregnancy and the mother gives birth successively to two or more Rh-positive babies who are only mildly affected.

TABLE III—RELATIONSHIP BETWEEN MATERNAL TITRE OF ANTI-RH AND CORD-BLOOD HÆMOGLOBIN LEVEL

Cord-blood Hb (g. per 100 ml.)	First-affected			Subsequently-affected		
	Frequency of cases at titre of:			Frequency of cases at titre of:		
	<1/10	1/10–1/20	1/40 or higher	<1/10	1/10–1/20	1/40 or higher
17·0 or over	32%	17%	10%	33%	4%	..
15·0–16·9	56·5%	34%	21%	67%	28%	21%
7·0–14·9	11·5%	45%	45%	..	68%	50%
6·9 and less	..	4%	24%	..	..	29%
No. of cases	44	79	42	6	25	17

Cord-blood Findings

Mollison and Cutbush (1949) have shown that the cord-blood hæmoglobin level provides a guide to the severity of hæmolytic disease in the baby. In addition, the cord-blood of most severely affected babies has an increased content of bilirubin. Tables III and IV demonstrate a close correlation between the titre of the maternal anti-Rh and the cord-blood hæmoglobin and serum-bilirubin levels, and provide further evidence that the clinical condition of the baby is related to the titre of the mother's antibodies when a carefully standardised indirect antiglobulin technique is used.

Optimum Time for Delivery

Now that most babies will recover from Rh hæmolytic disease if they can be delivered alive, premature delivery should be considered, at least until some more certain method of saving the baby is available, whenever the risk of stillbirth exceeds the combined risks of hæmolytic disease and prematurity. Our experience since 1955 has confirmed the claim of Kelsall et al. (1958) that the titre

TABLE IV—RELATIONSHIP BETWEEN MATERNAL TITRE OF ANTI-RH AND CORD-SERUM BILIRUBIN LEVEL

Cord-serum bilirubin (mg. per 100 ml.)	First-affected			Subsequently-affected		
	Frequency of cases at titre of:			Frequency of cases at titre of:		
	<1/10	1/10–1/20	1/40 or higher	<1/10	1/10–1/20	1/40 or higher
2·9 or less	73%	21%	2%	100%	16%	14%
3·0–3·9	21%	28%	18%	..	16%	0%
4·0–5·9	6%	24%	27%	..	29%	28%
6·0 and over	..	27%	53%	..	39%	58%
No. of cases	38	75	40	4	24	17

of the Rh antibodies in the mother's blood, determined by the indirect antiglobulin technique, is a good indicator of the likelihood of severe disease in the baby. By our technique, there is a considerable risk of stillbirth (approximately 1 in 4) when the mother's antibody titre has reached 1/40, whether or not there has been an affected baby at a previous pregnancy. The risk is certainly even greater when there has been a previous stillbirth from hæmolytic disease (Walker 1958). In consequence, therefore, we strongly endorse the recommendation of Kelsall et al. (1958) that a high titre of maternal anti-Rh is an indication for premature delivery of the baby.

First-affected Baby

In our series the risk of the pregnancy ending in a dead baby when the mother has not previously carried an affected child and has anti-Rh at 1/40 or higher has been as follows:

Duration of pregnancy (weeks)	*Risk of death (%)*
Before 34	3
At 34	5
At 35–36	3
After 37	20

This suggests that approximately two-thirds of stillbirths in first-affected babies might be prevented if the baby is delivered 21 days before full-term. Few other stillbirths are likely to be prevented unless the baby is delivered at, or before, the 34th week of the pregnancy; and this would undoubtedly introduce too many additional hazards from prematurity to be worth considering. Our current practice therefore is to recommend premature delivery 21 days before the expected date of delivery if

the mother's anti-Rh has reached, or exceeded, 1/40 by the 36th week of the pregnancy.

Premature delivery is not recommended if the antibody titre is less than 1/40 as the risk of stillbirth from hæmolytic disease under these circumstances is not great (only 1 case in 84 pregnancies in which the mother's anti-Rh was 1/10–1/20 and none in 59 cases where the titre was below 1/10). Moreover, at the 1/10–1/20 level, a third of the babies are so mildly affected as to require no treatment; and when the mother's titre was below 1/10, 85% of our babies were not transfused.

Subsequently Affected Baby

Our series is too small to support a policy of employing the maternal-antibody titre as the principal guide for premature delivery in cases where the mother has already carried an affected baby. Instead, and at least for the present, we prefer to employ the antibody titre as but one of several criteria which enable us to arrive at the difficult decision of whether, and at what time, the baby should be delivered prematurely.

In the 62 cases under review, there were 2 stillbirths in 32 cases where the maternal titre of anti-Rh was 1/10–1/20. Both were after the 37th week of the pregnancy. All 5 stillbirths, when the mothers' antibodies were at a titre of 1/40 or higher, occurred before this date.

When the mother has already had an affected child we can take into consideration the degree to which this child was affected. If the child was only mildly affected and did not require treatment, and if the antibodies are present at approximately the same titre as in the previous pregnancy, we anticipate that the present baby is likely to be only mildly affected and allow the pregnancy to proceed to term. Should the previous child have required treatment and the antibodies are at 1/10 or 1/20, or have risen from a titre below 1/10 in the previous pregnancy to a titre of 1/10 or 1/20 in this pregnancy, premature delivery is advised 21 days before full term. As table II shows, there is at this titre a risk of nearly 10% that the pregnancy will end in a dead baby.

When the titre is 1/40 or higher and the father is homozygous positive the risk of a dead baby is considerable (approximately 1 in 3). There is little or no chance of a mildly affected baby, and stillbirth, if it occurs, is generally before the 37th week. In such cases, therefore, we advise premature delivery 35 days before term. Premature delivery before 35 days is considered only when a previous child has been lost at, or before, this date of gestation. When the father is heterozygous-positive and there has been no change in titre during the pregnancy, a delay in delivery is recommended until 21 days before term in case the baby is Rh-negative. In all cases the size of the baby and the accuracy of the time of gestation are carefully considered by the obstetrician, together with all the other factors, in determining the optimum time for delivery.

Discussion

It has always seemed logical that there should be a correlation between the maternal titre of anti-Rh and the severity of hæmolytic disease in her baby, and that it should be possible to use the antenatal antibody titre as a guide to the management of the pregnancy. Freiesleben (1956), in a well-documented and thorough study, concluded that the antibody titre is of value as a guide to management if considered in conjunction with the history, and Kelsall et al. (1958) claim that fewer babies are lost from hæmolytic disease if labour is induced in mothers with a high titre of Rh antibodies. Amongst the reasons for a reluctance to accept this view are, we believe, the difficulty of obtaining consistent results by the indirect antiglobulin technique and the absence, until now, of an analysis of cases divided into first-affected and subsequently-affected babies. Our series shows that the indirect antiglobulin titre of anti-Rh provides a valuable guide to the prevention of stillbirth in Rh hæmolytic disease, but that different levels of titre should be regarded as critical according to whether the mother has, or has not, already carried an affected baby. We have found that there is little risk of stillbirth in a first-affected baby when the mother's titre is 1/10–1/20, but that, when there has already been an affected child so that the fœtus has been exposed to antibodies throughout the pregnancy, the risk is approximately 6% at this same titre. This is in agreement with Freiesleben's view that the history is of importance in determining a critical titre; and Kelsall et al. (1958) have, in fact, arrived at the same conclusion in recommending that a "titre index", compiled from the product of the maternal titre and the time during which antibodies are present, should be used as the principal guide to management. Their method, which necessitates that weekly or fortnightly tests of the serum of *all* Rh-negative mothers should be begun not later than the 26th week of the pregnancy, is, in our opinion, too cumbersome to be generally applied. By our method the critical titre is the maximum titre obtained at or before the time of gestation at which premature delivery might have to be considered. In first-affected babies, this is at approximately the 36th week.

TABLE V—OUTCOME OF 262 CONSECUTIVE CASES OF RH HÆMOLYTIC DISEASE IN THE BRISTOL AREA JUNE, 1955, TO DECEMBER, 1958

—	First-affected	Subsequently-affected	Overall
No. of cases ..	200	62	262
Stillborn ..	15 (7·5%)	7 (11·3%)	22 (8·4%)
Died	6 (3·0%)	4 (6·45%)	10 (3·1%)
Lived	179 (89·5%)	51 (82·25%)	230 (87·8%)

The techniques we employ to secure consistency in our antibody titrations are described in the appendix. We agree with Kelsall et al. (1958) that the indirect antiglobulin titre is a more reliable indicator to the clinical condition of the baby than other techniques using albumin-suspended or enzyme-treated cells. The indirect antiglobulin technique has the disadvantage, however, that it is difficult to obtain a close standardisation of end-points between laboratories, so that our critical titre of 1/40 may be expressed as a different result in another serological department. Whilst recognising that an eventual standardisation of end-points is most desirable, we do not believe that general application of our principles need be delayed until this is achieved. In our experience, there is a critical titre of anti-Rh, determined by the indirect antiglobulin technique, above which nearly all stillbirths in first-affected babies occur and 25–30% of mothers of first-affected babies possess anti-Rh at or above this titre. It should not be difficult therefore for a laboratory to determine its own critical titre by a retrospective analysis of its first-affected cases.

At present, premature delivery offers the only hope of preventing some of the stillbirths from hæmolytic disease of the newborn. On the practical side, however, the expected benefits of such a policy should be weighed against the risks of premature delivery—by induction of labour or by cæsarean section—known to exist under

the local conditions. In Bristol, experience with premature induction of labour has shown that minimal risks are involved with this method in expert hands, and premature induction is therefore practised in most of the selected cases. Cæsarean section has been resorted to only in a very few cases. It is beyond the scope of this paper to discuss the pros and cons of induction versus cæsarean section—a decision which in the end will depend mainly on local obstetrical practice and experience. As Walker et al. (1957) have stated, some severely affected babies must be anticipated as a result of early delivery, and special nursing care and an experienced team for exchange transfusion are prerequisites for the successful application of such a policy.

In a condition with so many clinical variables as hæmolytic disease of the newborn, it is possible to determine whether a change in management is significantly lowering mortality only by comparative analysis of a very large number of cases. The number of cases, especially first-affected babies, induced in Bristol according to maternal antibody titre are, as yet, too few for such an analysis. Table v summarises the outcome of the 262 consecutive pregnancies under review, however, and the number of these babies which have survived is approximately 88%. Walker (1959) gives the current expected chance of survival in this condition as 84%, and our findings do therefore suggest that our policy of a return to premature induction based upon the maternal titre of anti-Rh and the history may be saving lives.

Summary

Analysis of maternal titres of anti-Rh in 262 consecutive cases of hæmolytic disease of the newborn has demonstrated a correlation between the risk of stillbirth and the antenatal antibody titre determined by the indirect antiglobulin technique.

25–30% of mothers who have not previously carried an affected baby show a critically high titre of anti-Rh, and in such cases the risk that the pregnancy will end in a dead baby is approximately 30%. 2 out of every 3 stillbirths in these cases occur after the 37th week of the pregnancy, and it is therefore recommended that first-affected babies be delivered 21 days before term when the mother has a critically high titre of anti-Rh.

When the mother has already carried an affected baby the antibody titre during the pregnancy considered in conjunction with the severity of hæmolytic disease in the previous child is of value in determining whether, and at what time of gestation, premature delivery is indicated.

Some severely affected babies must be anticipated as the result of early delivery, and special facilities for nursing and transfusion are essential for the successful application of such a policy.

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Appendix

TECHNIQUE OF INDIRECT ANTIGLOBULIN TITRATION

During the time when premature induction for hæmolytic disease was discontinued in the Bristol hospitals, it was decided to limit the titration of maternal anti-Rh to 3 dilutions: neat, 1/10, 1/20. Antibodies demonstrable in the neat serum only were reported as "low titre", and those strongly present at 1/20 as "high titre". A retrospective analysis following the publication of Kelsall and Vos' (1952) paper suggested that the dilutions selected might prove of value in predicting the severity of disease in the baby. The practice of making an initial dilution of 1/10 was therefore continued and additional dilutions have been made by the generally accepted doubling-dilution technique.

Test Cells

A mixture of equal volumes of Group O Rh-positive red cells of genotype CDe/CDe and genotype cDE/cde is used. Blood from donors of these groups is collected twice weekly into anticoagulant acid citrate dextrose solution and stored at 4°C until used.

Technique

Samples of undiluted serum from Rh-negative mothers, and Rh-positive mothers with a suggestive previous history, are tested against enzyme-treated Rh-positive and Rh-negative cells at 37°C for the presence of Rh antibodies. Sera agglutinating the enzyme-treated cells are then titrated by the indirect antiglobulin technique.

0·2 ml. volumes of maternal serum or serum dilutions are placed in $3 \times {}^{3}/_{8}$ in. tubes at a titration range of neat, 1/10, 1/20, 1/40, 1/80. The 1/10 dilution is made by adding 0·1 ml. of serum to 0·9 ml. of physiological saline solution, using a graduated 1 ml. pipette. Serial dilutions are then made in normal saline solution by measured 0·2 ml. volumes from the same pipette, and 0·1 ml. of a 50% suspension of washed test cells is added to each tube. Following incubation at 37°C for $1^{1}/_{2}$ hours, the cells are washed and tested in the usual way against an antiglobulin reagent.

Controls

Besides the usual controls of the antiglobulin reagent, a stock anti-D serum of known titre (1/20 or 1/40) is included with each batch of titrations. Whenever possible, the previous sample of the patient's serum, stored at −20°C, is titrated also, as a comparative check.

On all occasions when a decision regarding premature induction is to be made on the result of the titration a duplicate "blind" titration at the 1/10, 1/20, and 1/40 dilutions is made by another member of the laboratory staff.

CEREBRAL DEMYELINATION ASSOCIATED WITH DISORDERS OF THE RETICULOENDOTHELIAL SYSTEM

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Åström, Mancall, and Richardson (1958) have recently drawn attention to an unusual neurological complication of disorders of the reticuloendothelial system, consisting of widespread, often confluent, foci of demyelination in the brain, with striking aberrations of neuroglial nuclei including many bizarre and gigantic forms. Their own three cases were associated with Hodgkin's disease and chronic lymphatic leukæmia, but comparable changes have also been described in association with a case of tuber-

culosis (Hallervorden 1930) and with one of sarcoidosis (Christensen and Fog 1955). The purpose of this paper is to record three further instances of this association, and to discuss briefly its clinical and pathological recognition.

Case-reports

THE FIRST CASE

A man, aged 55, was first seen at Guy's Hospital in April, 1951, complaining of a lump in the left groin. Biopsy showed Hodgkin's disease, and a block dissection of the left inguinal lymph-nodes was carried out, followed by local radiotherapy. Further courses of radiotherapy were given to the back and cervical lymph-nodes during 1953. A course of mustine (nitrogen mustard) was given in June, 1954, the total dose being 27·5 mg., and further courses of 35 mg. in January and 25 mg. in December, 1955. The hæmoglobin on the last occasion was 51%. A week after the last course of mustine he became forgetful and behaved strangely. On Jan. 24, 1956, he was able to reply to only the simplest questions. There was slight weakness and spasticity of the left arm, with increased tendon reflexes on the left. At times he did not appear to be fully aware of this side of his body. The cerebrospinal fluid (C.S.F.) was of normal composition and pressure. The electroencephalogram (E.E.G.) showed severe abnormalities, particularly in both frontal and the left occipital lobes. An air-encephalogram showed enlarged lateral ventricles. No significant abnormality was seen in the cerebral angiogram. Mental deterioration was rapid: he died 6 weeks after admission, after several days in coma.

Necropsy

(P.M. 8/6/56.) Outside the brain relevant changes were present in the spleen (650 g.), which was largely replaced by firm pale nodules, and in the lymph-nodes. The para-aortic nodes were large, firm, and rubbery, while those of the paraœsophageal and paratracheal regions were smaller but of the same appearance. No further dissemination of Hodgkin's tissue was found.

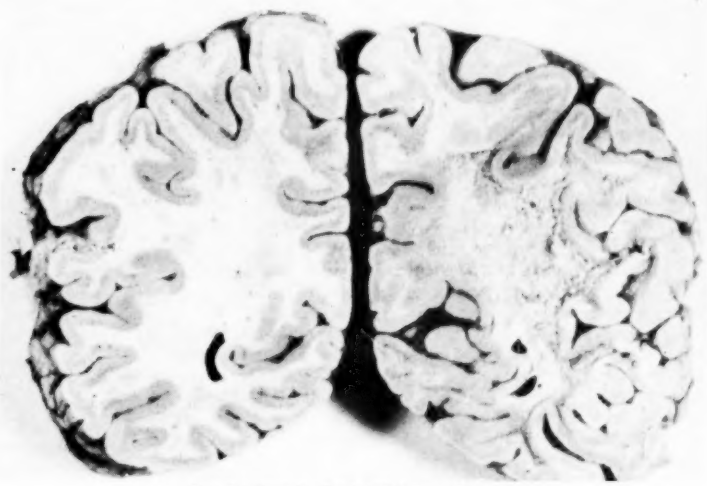


Fig. 2—Case 2. Occipital lobes of brain.

The *brain* (1480 g.).—The frontal lobes were symmetrically swollen and softened, but not congested. The white matter was softened, almost to a milk-jelly consistence—crumbly, yellow, and œdematous. The surrounding cortex appeared normal, and it collapsed as the œdema fluid seeped away. The right frontal lobe was the most affected (fig. 1), the change spreading up into the superior and middle frontal gyri, and becoming less confluent and more discrete on passing backwards. Further multiple, discrete and confluent, grey and yellow, areas were present in the upper half of the left frontal white matter—again becoming less numerous on passing backwards. Discrete foci of pinhead size, and slightly larger grey blotchy areas, were scattered in the parietal areas of both sides, in the right cingulate gyrus, in the right thalamus, and in the adjacent external capsule and the right temporal lobe. To a lesser extent, similar changes were found on the left side. The occipital and left temporal lobes, and the cerebellum, brain-stem, and spinal cord appeared grossly uninvolved.

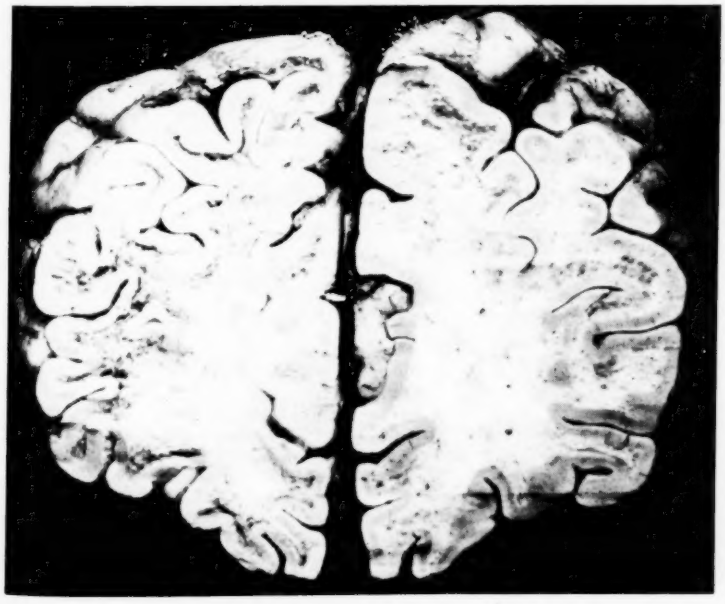


Fig. 1—Case 1. Frontal lobes of brain.

THE SECOND CASE

A man of 66, first seen in March, 1955, was complaining of lumps in the neck. He was found to have a generalised lymphadenopathy, splenomegaly, and a white cell-count of 290,000 per c.mm., with 99% lymphocytes. A course of radiotherapy, totalling 1650r, was given to the spleen and the mediastinal lymph-nodes. He remained well until April, 1958, when red papules, thought to be leukæmia cutis, developed on the legs. A further course of radiotherapy (290r) was given to the upper abdomen. In July he had visual impairment on the left, and a homonymous hemianopia with sparing of the macula. During the next 3 months he had increasing weakness of the left limbs. On admission to the London Hospital in November he was apathetic and confused. There was a severe left hemiplegia, with increased reflexes and extensor plantar response, left hemianæsthesia, and left homonymous hemianopia. There was no papilloedema, and the lumbar C.S.F. was normal. The blood-count showed a

hæmoglobin of 83% and white cell-count of 23,000 per c.mm. (lymphocytes 78%, polymorphs 26%). During the next 2 weeks there was increasing impairment of consciousness and some loss in the right visual field. From Dec. 16 a total of 1000r was given in 6 days to both sides of the head. No improvement occurred, dysphagia and dysarthria developed, and the patient died on Dec. 29.

Necropsy

(L.H.P.M. 434/58.) There was much enlargement (up to 5×2 cm.) of the upper and lower cervical lymph-nodes, and moderate enlargement of the paratracheal and carinal nodes. The cœliac, para-aortic, inguinal, and axillary nodes were all enlarged, soft, and white. The spleen was moderately enlarged (720 g.), but no definite macroscopic abnormality was seen in the bone-marrow.

The *brain* (1380 g.).—Most of the right occipital white matter showed creamy softening, the hind part of the lobe being partly collapsed, but the cortex was normal (fig. 2). Demyelination extended forwards into the right temporal lobe and the paraventricular white matter on both sides. The right frontal and left occipital white matter showed numerous discrete foci of pink and grey softening (0·1–0·5 cm.) merging in places to form larger irregular areas, often sparing the arcuate fibres. A similar focus (1 cm.) was seen in the right external capsule. The cerebellum, brain-stem, and spinal cord were grossly normal.

THE THIRD CASE

A man of 55, admitted to the London Hospital in October, 1958, was well until 2 weeks previously, when he became unusually quiet and was incontinent. When seen, he was sitting silently rubbing his unshaven chin or picking at his skin; he answered questions only occasionally, in monosyllables. Bilateral extensor plantar responses, and a mild right hemiparesis were present. There was no papilloedema. A large lymph-gland of fleshy consistence was felt in the right axilla. The blood-count was normal.

3 days after admission he became semiconscious. Bilateral frontal burr-holes were made: the right ventricle was tapped, and the C.S.F. found to be of normal composition and pressure. The E.E.G. showed marked bilateral abnormalities over the anterior cerebral region. Carotid arteriography was normal. Further attempts at ventricular puncture were unsuccessful. He became more deeply unconscious, and died 17 days after admission.

Necropsy

(L.H.P.M. 378/58.) Gross disease of the reticuloendothelial system was confined to the lymph-nodes of the right axilla, which were enlarged (up to 7×4 cm.) and had a pale pink and yellow mottled cut surface. The spleen (140 g.) appeared normal.

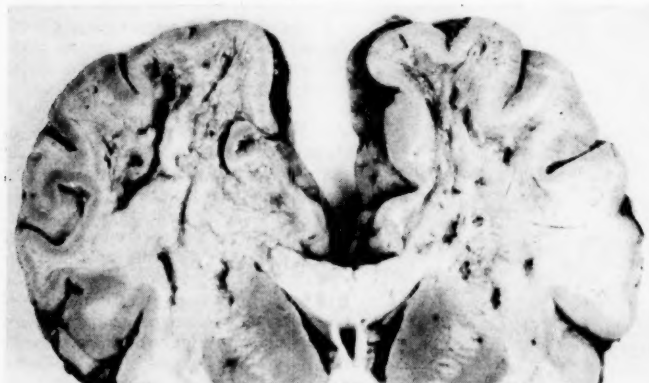


Fig. 3—Case 3. Frontal lobes, showing cavitation of the white matter, sparing of the arcuate bands, and swelling and damage of the corpus callosum.

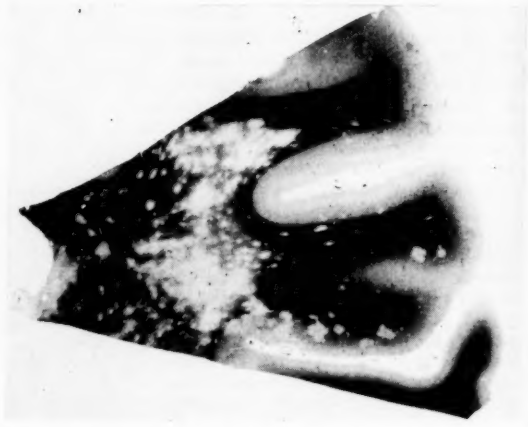


Fig. 4—Case 2. Multiple foci of myelin loss with confluence of large areas. (Loyez method. × 2½.)

The *brain* (1200 g.) showed symmetrical softening and cavitation of the white matter of the upper halves of the frontal lobes, and severe swelling and softening of the forepart of the corpus callosum. The cortex and the subcortical U-fibres around the areas of damage were conspicuously intact (fig. 3). The other regions of the cerebrum, the brain-stem, and the spinal cord appeared normal.

Microscopical Findings

RETICULOENDOTHELIAL SYSTEM

Case 1.—Much of the normal splenic architecture is lost, with the formation of numerous foci of Hodgkin's granuloma showing prominent Sternberg-Reed cells and other reticulum-cells, moderate fibrosis, and occasional eosinophil leucocytes. The splenic pulp shows numerous focal aggregations of histiocytes containing iron pigment. Plasma-cells are scanty both in the Hodgkin's tissue and in the splenic parenchyma.

Case 2.—The cervical, cœliac, and para-aortic lymph-nodes are diffusely infiltrated by small lymphocytes, with complete loss of normal architecture. Isolated strands of collagen are seen among the lymphoid cells, without capsular fibrosis. No plasma-cells or Russell bodies are present. There is much leukæmic infiltration of the portal tracts of the liver, and moderate diffuse and focal infiltration of the splenic pulp and bone-marrow by leukæmic cells. No infiltration in the kidney. Beneath the pleura of the lower lobe of the left lung is a poorly differentiated squamous carcinoma.

Case 3.—The normal architecture of the right axillary lumph-nodes is replaced by a diffuse proliferation of small lymphocytes interspersed with scattered foci of histiocytes, reticulum-cells, and occasional Sternberg-Reed cells. Well-marked fibrosis is present, both as coarse bands of collagen dividing the whole node and as numerous filaments and cords among the lymphoid cells. No eosinophil leucocytes or plasma-cells can be seen. The general histological picture is that of Hodgkin's disease, though not in its most typical form.

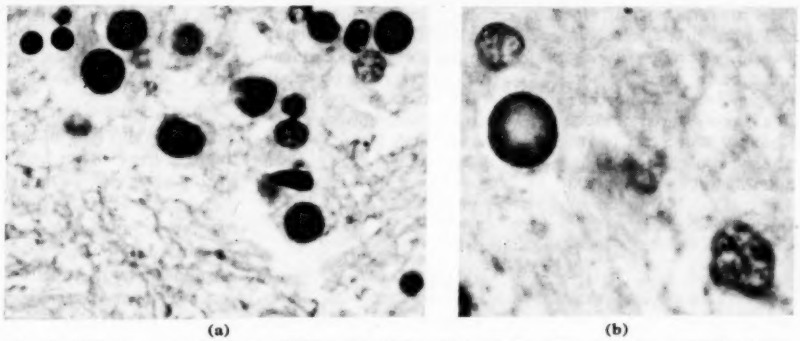
The only definite abnormality in spleen or bone-marrow is congestion and slight plasma-cell infiltration of the spleen.

NERVOUS SYSTEM: CASES 1 AND 2

Demyelinated Foci

In both cases the large confluent lesions are totally devoid of myelin sheaths, and the axons

within them are considerably reduced numerically; the exact amount of reduction is difficult to assess, however, owing to considerable separation of the structures by œdema fluid. The lesions are filled with loose masses of foam-cells containing sudanophilic lipids, and with fewer hyperplastic and swollen astrocytes. Capillary proliferation is slight. As the edges of the lesions are approached an increasingly dense feltwork of neuroglial fibres is found, which is most conspicuous in the right occipital lobe of case 2 (with the longer history). Neuroglial proliferation is seen for varying distances around the lesions, but the nerve-cells in the adjacent cortex, and the myelin sheaths both of the cortex and frequently of the subcortical U-fibres, are generally undamaged.



(a) (b)

Fig. 6—Case 2. Swollen basophilic oligodendroglial nuclei with smaller normal forms. (Hæmatoxylin and eosin. (a) × 750; (b) × 1200.)

The small isolated foci of demyelination (fig. 4) are less œdematous than the large ones. The myelin sheaths running through them are almost completely destroyed, while axons are apparently only slightly reduced. Evidence for degeneration of isolated axons, such as retraction balls, is found, however, in Bielschowsky preparations. Fat-filled macrophages are numerous, and proliferated and hypertrophied astrocytes also occur. Small foci sometimes encompass small blood-vessels, and perivascular hæmosiderin-containing macrophages are occasionally seen. Rarely, such small foci involve the cortex, and, more often, the basal ganglia, but the neurones in these foci are substantially normal.

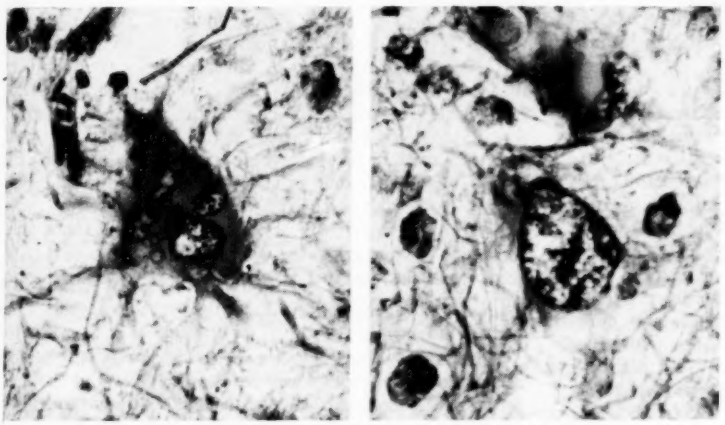


Fig. 5—Case 1. Abnormal giant astrocytic nuclei. (Hæmatoxylin and eosin. × 250.)

Small scattered lesions are present in the cerebellar white matter (case 1), and the brain-stem (case 2); one small focus is seen in the posterior column of the spinal cord of case 2 at the sixth cervical segment. The dorsal-root ganglia are normal.

Changes in the Neuroglia

Astrocytes.—In almost every lesion in cases 1 and 2 a variable proportion of the nuclei of the hyperplastic astrocytes show remarkable abnormalities (fig. 5). These consist of gross enlargement and increased affinity for stains, tortuous irregularities of form, micronuclei, mitotic figures apparently in prophase and metaphase (sometimes with considerably increased numbers of chromosomes), and increased numbers of nucleoli. The cytoplasm of these abnormal cells is not appreciably different from that of the more usual astrocytes with swollen clear cytoplasm (gemistocytes). No abnormal forms, such as those described above, are found in the tissue surrounding the lesions, although ordinary hyperplastic astrocytes often abound here.

Oligodendroglia.—In a wide zone of white matter surrounding the lesions are rounded, often deeply basophilic, nuclei with sharp outlines but blurred internal structure (fig. 6a and b), which are equally numerous in the two cases. With the Feulgen method they stain diffusely, though occasionally more intensely staining intranuclear granules are present. In form and distribution these nuclei resemble those of oligodendroglia, but are about twice their size. They excite no cellular reaction. Neither oligodendroglia nor these abnormal cells are present in the larger areas of damage; but in the smaller foci, while normal oligodendroglial nuclei are not seen, these abnormal nuclei are often to be found. Bodies of similar appearance are associated with the small lesions in the brain-stem of case 2, and the lesions in the cerebellar white matter of case 1.

NERVOUS SYSTEM: CASE 3

The damaged areas show total loss of myelin sheaths and conspicuous infiltration by lipid-laden foam-cells. The edges of the lesions are usually sharply demarcated, and the arcuate fibres are spared (fig. 7). In the corpus callosum, however, the edges of the lesions are sometimes blurred. At the edges of the large

Fig. 7—Case 3. Sharply defined edge of demyelinated area with preservation of subcortical fibres. (Loyez method. × 2½.)

areas there are small foci of damage. Small wide-spread isolated foci, as were observed in cases 1 and 2, are not present. Another distinguishing feature is the occasional presence in damaged zones of perivascular cuffing by small lymphocytes and sometimes plasma-cells. Astrocytic proliferation is pronounced, these cells being swollen and showing many fibrillary processes; but their nuclei, although large, are not grossly abnormal as in cases 1 and 2. Nor are the nuclear abnormalities, presumed to be oligodendroglial, detected in any region. No abnormalities are found in the remainder of the brain or spinal cord.

Discussion

CLINICAL FEATURES

All three patients developed a fatal neurological illness which progressed rapidly and without remission, and which showed no obvious relation to the stage and severity of the reticulosis. Clinical evidence of widespread bilateral cerebral damage eventually appeared. Dementia and pyramidal-tract lesions occurred in all, dementia being a presenting feature in two. Homonymous hemianopia, body-image disturbance, hemianæsthesia, and bulbar palsy were other notable symptoms. None of the patients had significant headache, papillœdema, or epileptic fits. The E.E.G.s showed widespread abnormalities over the parts of the brain clinically involved. The C.S.F. was normal. In most of these respects our patients resemble those described by Åström et al. (1958).

Although the clinical picture of this disorder is fairly distinctive, it must be differentiated from direct infiltration of the brain with leukæmic or reticulosis deposits, and from cerebral infarction. The normal intracranial pressure, the absence of lower-neurone cranial-nerve palsies or cord lesions, and the lack of response to radiotherapy, contrast with the clinical picture of infiltrative lesions of the brain. The steadily progressive course is unlike that seen in vascular thrombosis or hæmorrhage.

The resemblance of the illness to rapidly progressive Schilder's disease in adults is very close, and clinical differentiation probably cannot be made, particularly when the underlying reticulosis has not been diagnosed, as in our case 3. The pathological problems raised in this connection will be discussed later.

Like Åström et al. (1958), we have considered and rejected the possibility that the illness might have been caused by treatment. Although in case 1 neurological symptoms occurred within a week of a course of mustine, no such relation could be discerned in case 2, and in case 3 no treatment had been given. This does not exclude the possibility that some of the histological changes were caused by treatment, and this point will be discussed later. It is of interest that transient cerebral disturbances following mustine therapy in Hodgkin's disease have been reported previously (Bierman et al. 1949, Roswit and Pisetsky 1952).

PATHOLOGICAL FEATURES

The Demyelinating Process

In cases 1 and 2 the lesions were primarily multifocal, the areas of damage in the frontal lobe in case 1, and the occipital lobe in case 2, becoming confluent and massive as they developed. In the latter site the established fibrillary gliosis is consistent with the relatively longer clinical evolution of the disease, in which early involvement of the optic radiation was conspicuous. At the edges of the large areas of damage, and scattered throughout the brain and brain-stem were smaller foci, which, judging by their cellular content, were more recent, while very occasional minute clusters of microglial cells without evidence of demyelination were possibly, in agreement with Åström et al. (1958), the earliest form of the change. The histological appearances, therefore, suggest a continuous process progressing in time through the supervention of fresh lesions.

Most reported examples of this demyelinating process have been similar, and the terms " patchy " and " confluent " have often been used in the descriptions. The third case described here, however, shows a rather different pattern, closely fulfilling the histological criteria laid down for the diagnosis of Schilder's disease (Poser and van Bogaert 1956, Greenfield 1958)—namely, an essentially diffuse loss of myelin with sudanophilic breakdown-products, sparing to a greater or lesser degree the subcortical fibres. In case 3 the demyelinated areas were frequently sharply demarcated, whereas in cases 1 and 2 they were often not. There were also a few small isolated foci at the periphery of the larger lesion, but it is uncertain whether they arose separately or were merely digital extensions. The same difficulty is met in other reported cases of Schilder's disease, particularly in fulminating examples (Stewart et al. 1927 [case 3], Környey 1952). In these early forms a probable origin of the large diffuse plaques from the confluence of such foci has been suggested (Környey 1952, Poser and van Bogaert 1956, Peters 1958). Conversely, the massive confluence of small foci, seen in our second case and clearly illustrated in the first case of Åström et al. (1958), may result in a diffuse demyelination with sharp edges, difficult to distinguish from Schilder's disease; two of the previously reported examples were in fact interpreted as Schilder's disease by their authors (Bateman et al. 1945, Christensen and Fog 1955). According to Åström et al. (1958), however, these two cases did show the abnormalities in the neuroglial nuclei so characteristic of the others. This important feature was lacking in our case 3, making its position in this distinctive group less certain.

Nuclear Changes

The remarkable aberrations in the form of many of the astrocytes in our cases 1 and 2 are exactly like the changes found by Åström et al. (1958) and also those in all the other probable examples they gathered from the literature. While somewhat abnormal forms may occur occasionally in brain damage from any cause (Greenfield 1958), their constancy and frequency in these cases make this feature highly significant. Superficially the abnormal cells resemble malignant astrocytes. Yet their virtual confinement to the areas of damage, and their failure to multiply proportionately to the duration of the neurological illness, suggest that they are not invasive and multiplying units. We therefore agree with Åström et al. that they are probably not gliomatous.

The bizarre nuclear forms, in particular micronuclei, increased chromosome numbers, and abnormal mitoses, strongly suggest a pronounced disturbance of nucleoprotein metabolism, for similar changes frequently follow irradiation and the use of radiomimetic agents (Koller and Caserini 1952) in other tissues. Heavy doses of radiation may induce similar changes in the nuclei of neuroglia after a long delay (Arnold and Bailey 1954). While this explanation seems to be supported by the fact that our first case and several of the cases of Åström et al. were given radiomimetic drugs, similar changes were present in both Hallervorden's (1930) cases and in that of Christensen and Fog (1955), none of which received such therapy.

A third possibility is that of viral parasitism, although the evidence is tenuous. Åström et al. noted the presence

of eosinophilic inclusion bodies in both the abnormal astrocytic nuclei and in the basophilic and swollen oligodendroglial nuclei. We saw similar bodies in case 1, and a few of these were found to be Feulgen-positive, although they failed to stain with some of the standard stains for inclusion bodies.

Relation between Cerebral Demyelination and Lymphomata

Any discussion of this problem is highly speculative, but certain possibilities in the interrelation of the central nervous system and lymphatic tissue may be considered here.

The first possibility is that of a disturbance in normal immune mechanisms as a factor in the production of the cerebral lesion. This could occur in two ways:

1. Abnormalities of antibody production might involve the formation of autoantibodies. Hæmolysins and leucocytic antibodies may accompany lymphomata and lymphoid hyperplasia, and the formation of an anti-myelin antibody is a conceivable extension of this phenomenon.

2. The well-known reduction of normal immunity and resistance occurring with lymphomata might facilitate invasion of the central nervous system by an infective agent producing demyelination.

The second possibility is that of a metabolic disturbance primarily involving reticuloendothelial tissue and subsequently the white matter of the central nervous system. On present knowledge, the only possible mechanism in such a disturbance is one involving lipid metabolism, and particularly that of sphingomyelin. Thannhauser (1950) has suggested that in Niemann-Pick's disease the basic defect is an imbalance of enzymes in the reticular cell concerned with the metabolism of sphingomyelin, leading to an accumulation of this material throughout the reticuloendothelial system. If this explanation is correct, a tumour of the reticuloendothelial tissue might produce an accelerated degradation of sphingomyelin or related substances, and thus, possibly, a destruction of formed myelin-containing tissues.

Cameron et al. (1958) have reported a case in which acute neuropathy with demyelination of peripheral nerves was a terminal event in Hodgkin's disease. There was no infiltration of the peripheral nerves by Hodgkin's tissue. This case may possibly be related to the cerebral demyelination described here, but its position must await further examples.

Summary

Three cases of cerebral demyelination occurring during the course of Hodgkin's disease and lymphatic leukæmia are recorded.

In two the lesions in the white matter were multifocal and associated with curious changes in the nuclei of neuroglial cells. The syndrome appears to constitute a real entity.

The third case showed the picture of Schilder's disease.

We are indebted to Prof. Dorothy Russell for much help and encouragement in the preparation of this paper; and to Dr. R. R. Bomford, Dr. P. H. Tooley, and Dr. E. R. Boland for permission to publish cases 2, 3, and 1 respectively.

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References continued at foot of next column

ACUTE DISSEMINATED DEMYELINATION OF THE BRAIN ASSOCIATED WITH LYMPHOSARCOMA

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IN 1958 Åström et al. described three cases of an unusual multifocal demyelinating condition arising in the course of chronic lymphatic leukæmia and Hodgkin's disease, and they compared them with five similar reported cases. Three more cases of the same syndrome are reported by Cavanagh et al. (1959). The case we describe is of interest in that the demyelination occurred in the course of lymphoid follicular reticulosis (Brill's disease) which became lymphosarcomatous.

Case-report

A woman, aged 57, began to get dyspnœa and dropsy in March, 1957. In May, when she was admitted to hospital, there was enlargement of the liver and spleen, cloudy ascites (tapped), œdema up to the waist, right-sided pleural effusion, and enlargement of the axillary and cervical lymph-nodes, but no abnormality of the central nervous system. (Biopsy of the lymph-nodes revealed a lymphofollicular reticulosis with invasion of the capsule.) On June 3 the blood-count showed hæmoglobin 82%, with poikilocytosis and anisocytosis. She was discharged on July 22, but she returned several times for paracentesis abdominis. On Aug. 14 the hæmoglobin had fallen to 48%, with poikilocytosis, anisocytosis, and polychromasia, but no blast cells. In October, 1957, she complained of severe headaches. There was numbness down the left side of the body, with impaired sensation and diminished vibration sense below the left knee. Vision was impaired and there was right internal-ear deafness. She was readmitted to hospital on Nov. 11, 1957, and 5 pints of fluid were removed from the abdomen. She died next day.

Necropsy

The diagnosis was: lymphofollicular reticulosis and lymphosarcoma, with ascites and pleural effusion, pulmonary collapse, secondary anæmia, and acute disseminated demyelination of the brain; old amputation of the cervix and radium menopause (1947); uterine fibroids; cholelithiasis; hydronephrosis.

The external *lymph-nodes* were enlarged and still showed the follicular pattern of the primary disease, but the para-aortic, mesenteric, and right mediastinal nodes had fused to form large masses of lymphosarcomatous tissue invading the abdominal and pleural serosa, encasing the kidneys, and obstructing by pressure both venous and lymphatic return and the flow of urine in the right ureter. The pancreas was replaced by lymphosarcoma, and there were metastases in the lungs. The *spleen* (560 g.) was soft and purple, with large ill-defined follicles; there was moderate siderosis of the medullary histiocytes, but no sarcoma. The *femoral marrow* showed reactive (dark red) hyperplasia in the upper three-quarters of the shaft, with great increase in eosinophil myelocytes, small lymphoid follicles here and there, hardly any siderosis, and no metastases. The *liver* (2375 g.) showed passive central congestion

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and scattered foci of lymphocytes and histiocytes (sometimes in the portal systems but generally not), with slight siderosis of prominent Kupffer cells, but more siderosis in the histiocytes of the lymphoid foci.

The *brain* (1290 g.) appeared normal externally, but the cut surface showed multiple small dark pink areas (up to 0·2 cm. in diameter) in the cortex, subcortical grey matter, and pons, which were mistaken for metastases. Regrettably, therefore, the entire brain was not kept.

Fig. 1—Frontal lobe showing numerous discrete foci of demyelination in the cortex and white matter. (Heidenhain's myelin stain. ×5.)

Histology

The cerebral lesions consisted of small, discrete, well-defined foci of demyelination, and were found mainly in the deeper layers of the cortex and in the superficial parts of the subcortical white matter (fig. 1). A few similar lesions were seen also in the putamen. Although the axis-cylinders were relatively well preserved, in a few places they showed rarefaction and degenerative changes, such as beading and fusiform or bulbous swelling.

In sections stained for cells, the lesions formed well-defined, discrete, highly cellular nodules. In the smallest lesions the reaction was almost entirely microglial. In slightly larger lesions the microglia were mainly in the form of fat-granule cells, and there was also an intense astrocytic reaction. The astrocytes were mainly of the large protoplasmic variety, some containing more than one nucleus, and occasional mitotic figures were seen. The largest lesions in the white matter contained in addition bizarre giant astrocytes, some mononuclear and others multinucleated (fig. 2). Some nuclei showed a typical vesicular structure with scanty chromatin, others were very dense and hyperchromatic, and others consisted of a ring of small chromatin granules with an ill-defined nuclear membrane. No inclusion bodies or abnormal mitotic figures were seen in the giant cells. Small compact nuclei, resembling those of oligodendrocytes but slightly larger in diameter, were present also, though inconspicuous. No glial fibres were demonstrated.

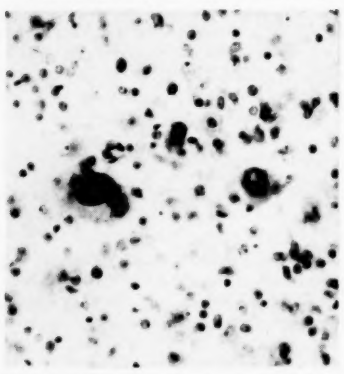

Fig. 2—High-power view of one of the foci showing intense glial reactions including two giant astrocytes. (Carbol azure. × 320.)

The blood-vessels showed only slight reactive changes, such as swelling of the endothelium, thickening of the adventitia, and minimal round-cell infiltration, mainly microglial in origin.

Discussion

The syndrome of acute disseminated demyelination of the brain with reticulosis, described by Åström et al. (1958), has not previously been reported either in Brill's disease or in lymphosarcoma, although there is clinical evidence of neurological complications in the course of these conditions (Sparling et al. 1947, Hutchinson et al. 1958). In our case symptoms and signs of involvement of the nervous system appeared only a month before death. The lesions suggested an early stage in the development of the condition: they were small, discrete, and confined mainly to the junction between the cortex and white matter, the basal ganglia, and the brain-stem. Histologically the lesions were typical of the syndrome, showing focal breakdown of myelin, with microglial phagocytosis, preservation of axis-cylinders, and a bizarre glial reaction.

The pathogenesis of the condition is obscure, and little can be added to the original authors' discussion. But the possibility of an antigen-antibody reaction may be suggested. The appearance of immune autoantibodies, particularly hæmolytic ones, in the course of the reticuloses is well known. Whilst this aspect was not examined during the patient's life, the presence of hæmosiderin deposits in the spleen, lymph-nodes, and lymphoid aggregates suggests that a hæmolytic element may have played a part in the anæmia. The possibility that myelinolytic autoantibodies may be produced also in some reticuloses requires further investigation.

Summary

A woman, aged 57, with lymphofollicular reticulosis and lymphosarcoma, developed signs of involvement of the central nervous system a few weeks before death.

Postmortem examination of the brain revealed acute multifocal demyelination of the cerebral cortex, white matter, basal ganglia, and brain-stem, with a bizarre glial reaction.

The lesions appeared identical with those previously described in Hodgkin's disease and chronic lymphatic leukæmia.

Our thanks are due to Dr. J. E. Cates for access to his clinical records, to Prof. T. F. Hewer for his interest, and to Dr. R. M. Norman for his help and criticism.

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ON ROUTINE BARIUM EXAMINATION OF THE SMALL BOWEL

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". . . routine requests for 'barium meal and follow through' have no justification." (Pygott 1958)

"The examination is wasteful of time, energy, and material and might well be abandoned as a routine test." (Glendinning 1958.)

Many will agree with these opinions, especially if "routine" is taken to mean "done regularly after examination of the stomach in case something abnormal can be detected in the small or large bowel".

Lesions of the foregut and hindgut are more common than those of the midgut; but the midgut is the most important part of the alimentary tract, and the small bowel is the only part we cannot do without. The radiological appearances of the various disorders and anomalies arising therein are beautifully illustrated in an abundant literature,

mostly of well-established and advanced cases. Specialised techniques, some requiring intubation, have been developed to display them to the best advantage, and in certain centres the simpler methods have been superseded.

It seems to have been overlooked, however, that in many busy X-ray departments serving general hospitals there is a need to try to separate the many normal from the very few abnormal cases. There is still, I believe, a place for routine follow-through in patients suspected of having a lesion of the small bowel or ileocæcal region, the word " routine " implying that the examination is done during regular barium sessions without any special procedure.

The following is an account of an inquiry into the value of such " routine " examinations done in the Western Infirmary, Glasgow, during 1957. Suggestions are made for improving results by simple methods.

How Useful is Routine Follow-through?

The relevant files of the X-ray department and the hospital records office were examined. I deliberately excluded requests for estimation of gastric emptying-time—e.g., in suspected pyloric stenosis (this being really an extension in time of examination of the stomach), and also cases of gastrojejunal anastomosis, unless follow-through was specifically requested.

190 patients were found: more were referred by physicians (106) than by surgeons (84); more were outpatients (120) than inpatients (70); and there were more women (107) than men (83).

Of the 190 patients, 31 had been given a motility meal six hours before the usual barium-meal examination of œsophagus, stomach, and duodenum—a procedure perhaps more suitable for private than for routine hospital practice. The remaining 159 had a barium examination of the upper alimentary tract in the morning with one or more films taken as necessary. They were screened again in the morning, and later before or after the afternoon barium session (often by a different radiologist), more films being taken as required. Only 34 had twenty-four-hour films.

Thus the methods used by eight radiologists fell midway between the simplest form of examination, in which only one or two films are taken after the meal, and the more extended examination where films are taken hourly during the morning and afternoon, with additional screening and twenty-four-hour films as a routine.

WHAT WAS FOUND?

Most requests were for suspected lesions in the right iliac fossa and for suspected bowel obstruction; after these came diarrhœa, malignancy, and unexplained anæmia. My original intention of analysing the results in these groups had to be given up because of the difficulty of knowing what was in the minds of the clinicians when they asked for follow-through, and because of the various combinations of symptoms and signs encountered. So, confining attention to definite entities, this is what I found:

Of 17 cases of known or suspected *Crohn's disease*, 11 were subsequently diagnosed differently, leaving 6 undoubted cases. Of these, 5 were reported as abnormal, and only 1 was missed. This was a subacute case found to have a thickened terminal ileum at operation a month before X-ray examination, and again when resected a month later.

Of 13 cases of suspected *steatorrhœa*, 3 were later unsubstantiated, and 10 were regarded on clinical grounds as having steatorrhœa. Of these, only 2 were picked up at follow-through, and 8 were reported normal.

In neither of these groups was any case detected which was not already suspected clinically.

Of the remaining 160 examinations, only 4 were abnormal and these can hardly be called diagnostic triumphs for the follow-through procedure:

1. A case of *small-bowel obstruction* in which a dilated small bowel and fluid levels were found, so follow-through was no more helpful than plain films. An adenocarcinoma of jejunum was found at operation.
2. Dilatation of the proximal ileum in a case of *post-gastrectomy anæmia*, the only one positive (and only just) in 7 such cases in which a source of bleeding below the stoma was being looked for.
3. Duodenal stasis in a case of *duodenal obstruction* by superior mesenteric vessels, which should not have required follow-through.
4. *Diverticulitis* of the colon.

Thus only 11 cases out of 190 were reported as in any way abnormal.

WHAT WAS MISSED?

From the case-sheets of the 190 patients (less 14 whose records are not available) there were six conditions which might have been shown up by follow-through.

1. A man with the *blind-loop syndrome*. He had had an enteroanastomosis in 1953 after obstruction caused by adhesions from a previous appendicectomy. His follow-through was reported negative, but when he died three months later he was found to have only 7 feet of functioning bowel.
2, 3. Patients with *subacute obstruction* from inguinal hernia.
4. A very large *carcinoma* of the head of the pancreas.
5, 6. Patients with *Meckel's diverticulum*.

Since I saw the clinical summaries (January, 1959) others may have come to light. The above 6 patients, the 8 patients with steatorrhœa, and the patient with subacute Crohn's disease—15 in all—had something abnormal about the small bowel which escaped detection.

I do not suggest that they all could or should have been picked up, but it is fair to conclude that in this hospital during 1957 more conditions of the small bowel were missed by routine follow-through than were detected; and, as stated above, none was found which was not already suspected clinically.

DISCUSSION

Assuming accurate coding of diagnosis, it seems that only 6 patients with small-bowel disorder (2 each of Crohn's disease, steatorrhœa, and small-bowel tumour) were seen in the hospital during 1957 without having a follow-through examination.

Only 13 of the case-sheets mentioned that occult blood in the stools had been looked for.

So it may be assumed that when some clinicians suspect the integrity of the small bowel in cases other than those of acute abdominal emergency, they turn to, and rely on, the radiologist for guidance.

The help given to the clinician, in the management of an individual patient, by a normal result from this examination must not be forgotten, or undervalued. The number of negative results is unimportant if the method is reliable in detecting disorders of structure and function, particularly in the early stages, however infrequently they occur. Nevertheless my results confirm the general impression that the procedure is unreliable.

It is also inconvenient to all concerned.

Consider the *patient* first, as we always should. He or she has to be available all day, often without being forewarned, and there is a limit to what even friendly neighbours can do for young children or old people at home. There may be children at school or a husband coming home for dinner. Sometimes long bus journeys with cross-connections have to be made, and perhaps repeated the next morning. There are seldom facilities for the patient who had only barium for breakfast to

have a more orthodox lunch. This is all borne willingly by the patient, because he thinks that the procedure is both necessary and helpful.

More important, if many large films are taken of the abdomen in addition to repeated screening, the radiation hazard to the gonads must be weighed against the possible benefit of the examination.

Smooth working of the *X-ray department* is inconvenienced by intermittent screening, and large films are expensive.

The *radiologist* on a sessional basis is seldom able to finish the examination himself, or he may have to interrupt a reporting session later to adapt his eyes for further screening. As Zimmer (1958) says " It may well be that the delay in completing the examination and the circumstances under which it is completed account for some of the conditions being missed."

Follow-through is not a popular procedure with radiologists who are aware of its shortcomings; but some clinicians do not know how perfunctory it can be, or cannot properly assess the observations recorded. Where the ideal of close collaboration is not realised—and under routine conditions it is not—it is often difficult to know the clinicians' thoughts, despite the snippets of history entered on request forms. Detailed knowledge of the patient is necessary if different procedures are to be adopted for different problems, as recommended by Pygott (1958).

Thus the chief drawback to simple procedures at the present time is that they are long-drawn-out, with necessarily intermittent and momentary examination of a continuous process. On the other hand special procedures are not suitable for routine use. What is wanted is a quicker method, if possible one which also shows mucosal detail more easily for the detection of early changes, and which produces better filling of the whole small bowel.

What Can be Done?

The answer is likely to be found in one of the many techniques for accelerating the passage of barium through the small bowel.

For this purpose, many agents have been used, including barium warm and cold; barium in water, in isotonic saline, or in water with a pinch of salt added; barium followed by ice-cold water, either at once or in fractions; barium with purgatives, with morphine, ipecacuanha, or insulin; and recently follow-through combined with oral cholecystography, each accelerating the other.

The results of Weintraub and Williams (1949) are striking. Of 78 cases (including 2 of sprue, 5 deficiency states, and 3 of Crohn's disease), 90% had the head of the meal in the cæcum or beyond in under one hour, and indeed in 50% the transit-time was between five and fifteen minutes.

They used a fractional method, giving 4 oz. of barium in 4 oz. of isotonic saline at room temperature, followed by 8 oz. of ice-cold saline. One 17 × 14 in. film was taken after five minutes, a further 8 oz. of ice-cold saline was given, and two more films were taken fifteen and thirty minutes from the first. These were shown to the radiologist, who would screen and take spot films as required.

The " club soda " technique of Bendick (1954) requires a less exacting time-table, and has other uses. He uses 7-oz. bottles of soda-water (ginger ale for children), and after being cooled in a refrigerator the contents are drunk through a straw.

Following Bendick's lead, I have found ordinary soda-water, uncooled, useful in barium examination of the œsophagus, stomach, and duodenum. It is the modern substitute for Seidlitz powder, being less clumsy and cheaper.

Soda-water can be used in routine barium work:

1. *To make an air bubble* when there is none, to demonstrate the gastric fundus. I have used it to show the left dome of diaphragm in a case of opaque hemithorax, and for localising foreign bodies.
2. *To increase the normal air bubble* for better mucosal detail by double contrast, particularly in lesions of the gastric fundus and cardia, and around a stoma. The duodenum in hypersthenic patients can sometimes be seen better through a pyloric " window ", and help can be obtained in deciding whether pyloric stenosis is due to a lesion proximal or distal to the pylorus.
3. *To stimulate gastric peristalsis* by the increased bulk of fluid.

These are only some of the possible uses of soda-water in barium work, and it is useful to have a siphon at hand for use as required. When a follow-through is on the list, the siphon is cooled by ice or in a refrigerator half-an-hour beforehand.

The rationale of the technique lies mainly in the increase of bulk of the gastric contents with consequent peristalsis, and in the dilution of the opaque medium in the bowel. If advantage is also taken of the effect on gastric emptying produced by lying prone—well known to radiologists but less known by others—regular and sustained gastric emptying is obtained. This is the main physiological factor in promoting even filling of the small bowel, and the pattern obtained is best when this is rapid. The soda-water is rapidly warmed in the gut, but the effect on gastric peristalsis persists, and the increased bulk of the intestinal bolus does the rest.

Basic Principles

Radiological observations are concerned mainly with (1) transit time, (2) structural integrity, and (3) mucosal pattern.

Transit Time

The limits of normal are ill-defined and somewhat elastic. Shanks (1958) says: " The average time taken by the head of a barium meal of average amount to reach the cæcum is, in the writer's experience, $1\frac{1}{2}$ to 2 hours, and times between 1 to 4 hours should be considered normal." Yet I have found that times of from one to even six hours tend to be reported as intestinal hurry whenever the clinical history suggests this might be present.

Although Bendick's technique takes advantage of the three main physiological factors (regularity and frequency of gastric emptying, consistence of the medium, and the degree of concentration due to water absorption), there are three other non-physiological factors which tend to invalidate transit time as a guide to function.

First, the quite *abnormal conditions* of the examination. After a period of waiting the patient, hungry and anxious, is led into a room dark and charged with electrical mystery. He is given a wholly indigestible potion which tastes only too like the rare earth it is, and which is rightly treated as a foreign body. His inner workings are then laid bare for inspection by total strangers. In these circumstances, trying to be physiological by using isotonic saline, seems to be an unnecessary refinement; any accelerator which does not produce artefacts may be used.

Second, the widely varying natural differences in intestinal behaviour are well known to be modified by the presence of *disease*.

Third, the wide *anatomical variation* in the length of the small bowel is not always remembered. This has been described by Underhill (1955) and many others. Hirsch et al. (1956) found a mean length in 10 normal adults of only $8\frac{1}{2}$ feet, and indeed, Alvarez (1940) gave 8–10 feet as the normal length from mouth to anus. The difference between in-vivo measurements and those made by pathologists and

anatomists, ranging from 10 to 40 feet with a mean of 21 feet, is of course due to muscle tone.

Hence observations on transit-time are only of value when the normal for the patient is already known, as in comparative studies of the action of drugs.

The danger lies in the common assumption that the rate of passage of food will be similar to that observed with barium. That the bowel handles them differently has been known for a long time (since the work of Alvarez and Barclay)—even when they are mixed, as has been confirmed by more recent workers, quoted by French (1952).

We may conclude that the loss of observations on transit time is more than balanced by the gains resulting from acceleration.

Structural Integrity

Weintraub and Williams (1949) concluded that distribution of barium along the bowel was as good with ice-saline as with the conventional follow-through, and in several the terminal ileum was better filled. French (1952) says the accelerated techniques give better filling, so that the chances of detecting changes in calibre and other organic abnormalities are better.

Mucosal Pattern

Because of better dilution in the ileum there is less clumping, and so there is better mucosal detail extending right down the ileum. It is now widely known that clumping is not a sign of hypersegmentation, disordered motor pattern, or deficiency state, but an artefact produced by changes in the diluent—especially excess mucus. The best mucosal pattern is therefore obtained when non-flocculable barium is used. The use of such a barium suspension is necessary if soda-water is given as well; for otherwise clumping quite often occurs in the ileum.

Most of the cases of steatorrhœa met with in this country are suspected because of some sign of malabsorption, and it must be rare outside special centres for a patient to be encountered with the condition so advanced that a characteristic radiological picture will be obtained with an ordinary barium suspension. Hence I suggest that a technique which uses non-flocculable barium to permit study of mucosal detail right down the ileum, in *all* patients, will be more satisfactory.

Own Experience

During the last three months of 1958, I examined 43 patients.

The siphon was cooled in a bucket of crude ice half an hour before examining the œsophagus, stomach, and duodenum in the usual manner with a third of a pint of 'Raybar' diluted with another third of a pint of tap-water. Then a quarter of a pint of soda-water was given. Usually prompt gastric peristalsis appeared, but some stomachs dilated to accommodate it, to empty once the patient turned prone.

All were examined under routine conditions, taken as they appeared during the barium sessions. No special arrangements were made, and the quantities used and the amount of trolley space available for leaving the patient lying prone varied.

I soon learned the importance of the water being really cold, of the patient lying prone, and only later of the need for a second or third drink at short intervals to get the quickest results. Usually, the patient was seen half an hour and one hour after the first cold drink, to study the mucosal pattern, and thereafter as necessary till the terminal ileum and ileocæcal junction had been palpated at fluoroscopy.

6 patients took between four and six hours for completion, 10 took between two and four hours, 7 between one and two hours, and 12 were completed in under one hour, half of them in under thirty minutes. The remaining 8 were also finished in under an hour, but before the cæcum had been reached. Put another way, over 60% of these patients were on their way home or back to the ward in under two hours, having had their upper and middle alimentary tract examined more thoroughly than in the usual way. All except one were reported normal, and so far as is known (January, 1959) nothing was missed.

Though nothing like as good as those of Weintraub and Williams, these results are encouraging, and it is hoped that others may be stimulated to use one of the acceleration methods. They are readily adaptable to the radiologist's individual requirements, they are convenient to all concerned, and they are better suited to picking up disorders of structure of the small bowel under routine conditions than present methods of follow-through.

> "If it were done when 'tis done, then 'twere well
> It were done quickly." *Macbeth*

Summary

Dissatisfaction with routine barium-meal and follow-through examination is widespread. Methods vary widely, but even when a simple one is used (and only for patients with suspected lesions of the small bowel or ileocæcal region) the examination is unreliable and inconvenient to all concerned.

Nevertheless, there is a place for routine follow-through of patients in a general hospital where separation of the many normal from the very few abnormal cases is the object. Specialised techniques, some requiring intubation, are not suitable for this purpose, however necessary they may be for the detailed examination of selected cases.

Of many methods of accelerating the passage of barium already described, two are given in detail, those of Weintraub and Williams (1949), and of Bendick (1954). Well-founded on basic principles, they have worked well in the hands of their originators, yet have not been widely adopted.

Bendick's use of soda-water is particularly useful in examination of the stomach and, when cooled, as an accelerator. The gains of better mucosal detail, and better filling of the whole small bowel, with personal examination of the ileocæcal region—which should increase the chances of picking up early changes in structure—more than make up for the loss of transit-time observations as a guide to function. More reliable, such methods are also more convenient.

Of 43 cases examined personally by Bendick's method modified to suit local conditions of work, over 60% were on their way home or back to the ward in under two hours.

This is encouraging. Others may well be even more successful, to the mutual benefit of radiologist and patient.

I wish to thank all who assisted in this work, and particularly Dr. S. D. Scott Park for providing facilities, encouragement, and help.

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SERUM-CHOLESTEROL, DIET, AND CORONARY HEART-DISEASE IN AFRICANS AND ASIANS IN UGANDA

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IN the African population of Uganda coronary heart-disease is almost non-existent. This statement is confirmed by adequate necropsy evidence (Davies 1948). In the Asian community, on the other hand, coronary heart-disease is a major problem. During the three years 1956–58 the Kampala health department registered 102 male and 45 female deaths over 30 years of age among Asians and of these 48 (44 male and 4 females) were certified as due to coronary heart-disease (" myocardial infarction ", " coronary thrombosis "). Though the errors inherent in certification must be borne in mind, it is noteworthy that 43% of male deaths and 9% of female deaths over 30 years of age were attributed to coronary heart-disease.

While the significance of a high serum-cholesterol level in the pathogenesis of coronary atherosclerosis cannot yet be taken as proven, it is supported by much indirect evidence.

In a survey of a multiracial community in Cape Town Bronte-Stewart et al. (1955) have shown that wide differences in the incidence of coronary heart-disease in different races may be associated with a parallel difference in the mean serum-cholesterol levels. Moreover the report of a prospective study (National Advisory Heart Council 1956), in which blood-lipid measurements were made in healthy men who were then observed for two years, establishes clearly that elevation of blood-lipids precedes clinical coronary disease and that mean serum-cholesterol concentrations appear to have a high predictive value for populations; although this cannot be applied to the clinical prediction of coronary heart-disease in the individual.

In view of the radically different incidences of coronary heart-disease in the two communities in Kampala and their marked differences in social, economic, and dietary backgrounds, we decided to measure serum-cholesterol concentrations in African and Asian males at three age-levels—viz., 12 years, 20 years, and over 40 years.

Socio-economic Background

Kampala is the largest town in the Uganda Protectorate with some 50,000 inhabitants (25,000 Africans, 20,000 Asians, and 5000 Europeans). It lies on a group of hills about 4000 ft. above sea level, and the temperature varies from 65 to 80°F by day with little seasonal variation. The rainfall is about 50 in. a year and the relative humidity is 60–80%.

African

The Africans live mostly in the peripheral areas of Kampala where they are predominantly agricultural smallholders growing most of their own staple foods and cash crops such as cotton and coffee.

The Baganda are the original inhabitants of the area and most have a small farm on the outskirts of the town; they form the middle and upper classes in local African society, but the majority are simple peasants. The immigrant peoples from Ruanda-Urundi and the Western Province tend to be employed in unskilled and menial work and are at the lower end of the socioeconomic scale. The people attending Mulago Hospital outpatient department generally belong to the less economically successful sections of the Baganda and to the immigrant groups from other parts of the Protectorate and Ruanda-Urundi.

The dietary habits of all groups depend partly on their purchasing-power and partly on traditional customs. In general two meals are taken daily—midday and late evening—and food distribution appears to favour the males. Where the man is at work all day, and in all the poorer groups, a single evening meal is taken. The staple foods, green plantain and sweet potatoes, are steamed in banana leaves; cassava, yams, maize, and millet are also staple commodities, in particular of the non-Baganda groups, while pumpkins, tomatoes, and green leafy vegetables are taken by all. The adequacy of protein in the diet depends almost entirely on the extent to which pulses, groundnuts, and cereals are used. Most meals are served with a sauce made of groundnuts, beans, and a mixture of vegetables, and occasionally meat or fish, and these are fried in very small amounts of fat. The difference between the diets of the moderately well-off and the rich seems to reside in the quantity and quality of the sauces rather than in the quantities of the staple foods. When the Baganda can afford to do so they eat considerably more fat than is usually recorded, and eat it mainly in their sauces (Schwartz and Dean 1955). In the typical adult attending Mulago Hospital the daily fat intake is 16–20 g., while well-to-do families on housing estates take up to 40 g. daily with a total daily intake of about 2000 calories. Even in middle-class urban families meat is eaten only once or twice a week, and in the labourer class perhaps only once a month.

Asian

The Asian community in Kampala is derived mainly from immigration from the north and west of India, augmented by natural increase over the past fifty years. The Asians provide most of the skilled labour and business enterprise and are a major source of professional skills. This community is on the whole economically prosperous as compared with the Africans, and, while the range of financial status is wide, there are few families who cannot afford to eat reasonably well. Kampala has twice as many Hindus as Muslims, and these religious differences are closely associated with differences in diet and alcohol intake, the Hindus being by tradition vegetarians and taking no alcohol. They are in fact lacto-ovo-vegetarians, and eggs are eaten in small quantities in most families, especially by the men. The Muslim diet differs in that meat, fish, and poultry are taken and eggs are more freely used.

The basic foods are polished rice, " dhal " (lentils), wheat flour (for making " chapatis " [handmade unleavened breads] and " pooris " [unleavened bread fried in oil]), green vegetables and herbs, and other vegetables and fruits. Fats and oils are always used in the preparation of foods, and cottonseed oil and " ghee " are mainly employed, together with smaller quantities of butter and groundnut oil. The " ghee " (clarified butter) available is either a " superfine " form, made from pure dairy products, or one made from vegetable fats. Both types are widely used in Kampala, the dairy product somewhat more commonly, while a few better-off families make their own ghee in large amounts from Kenya butter. As ghee is relatively expensive the proportion of cottonseed oil to ghee used may be greatly increased in the poorer families. The cottonseed oil is made locally and is used for frying

vegetables and breads, while ghee is used on chapatis, in boiled rice, and for preparing vegetables and sweetmeats. In this particular survey the average estimated quantities of fats taken per person weekly are: 1 lb. (454 g.) cottonseed oil; $^1/_2$–$^3/_4$ lb. (230–340 g.) ghee; $^1/_4$ lb. (114 g.) butter; 6–8 pints milk; and 1 oz. (30 g.) cheese. It is evident that fats and oils provide a large proportion of the total caloric intake in the Asian community whatever the religious or dietary group. The estimated daily intake of fat, excluding that contributed by meat, is estimated at 30–45% of total caloric intake.

Selection of Subjects

The selection and matching of comparable groups at various ages in the African and Asian communities presented many problems.

Within the Asian group religious and sectarian differences are associated with differences in diet, while in the African community the rapidly changing social and economic patterns of a developing society make it almost impossible to select groups at the various ages who could be said to represent a steady progression along the " normal " pattern of a particular society. In their childhood and youth those in the over-40 group have certainly experienced a nutritional background far less favourable than that which obtains in schoolchildren and students of today. These latter groups in turn will contribute largely to the new middle and professional classes with a nutritional standard far above that found in the present over-40 group.

Africans

(*a*) *12-year group.*—96 children were selected from two boarding-schools near Kampala; most were Baganda and few were from really poor families. The average age was 11·8.

(*b*) *20-year group.*—New students entering Makerere College, who had spent three to six months at home on local diets, were examined and bled within three weeks of arriving at College, and 101 unselected sera were used. The students came from all three East African territories and a wide variety of tribes. The average age was 20·3.

(*c*) *Over-40 group.*—120 men were selected from outpatients attending Mulago Hospital for minor complaints. There were 61 Baganda, 22 Ruanda, and 37 from other tribes. The average age was about 50. All appeared to be in good health and none had been admitted to hospital or referred to consultant clinics. If any bias in selection existed it was towards excluding any who looked thin or malnourished.

Asians

(*a*) *12-year group.*—120 children were selected from two Kampala schools; most came from one Muslim school and were non-vegetarian. The average age was 12.

(*b*) *20-year group.*—104 students were bled from five Kampala schools. Two-thirds were non-vegetarian, and the average age was 19.

(*c*) *Over-40 group.*—141 men were selected by general practitioners in Kampala from persons attending their surgeries for minor complaints. 11 subjects known to have diabetes mellitus or coronary heart-disease were excluded. Of the remaining 130 subjects, 94 were vegetarian and 36 non-vegetarian, a bias introduced by the larger number of Hindu doctors in general practice. The average age was 49.

Methods Used

Most specimens were collected early in the morning. In the Asian over-40 group specimens were usually collected in the evening, about four or five hours after the midday meal and before the evening meal.

A light tourniquet was applied, and venous blood was collected using a hypodermic needle size 0 (length 41·5 mm.), to which was attached a length of translucent plastic tubing. When clotting had occurred the clot was loosened from the walls of the tube and the tube centrifuged. Serum was separated and stored at minus 10°C until used; all testing was completed within ten days of collection. The method of Sacket as described by King (1946) was used to determine serum-cholesterol.

TABLE I—MEAN SERUM-CHOLESTEROL CONCENTRATIONS IN AFRICAN AND ASIAN MALES, KAMPALA, UGANDA

Age (yr.)	Serum-cholesterol (mg. per 100 ml.) (mean & S.D.)	
	African	Asian
12	(96) 166 ± 40	(120) 206 ± 46
20	(101) 164 ± 28	(104) 218 ± 49
40	(120) 145 ± 43	(130) 248 ± 52

Numbers in parentheses are numbers of subjects in each group.

The standard error of difference between means (S.E.D.) and the difference between the means (D.) was calculated; where D./S.E.D. was greater than 2, the series were considered significantly different (Chambers 1955).

Findings

The mean serum-cholesterol levels and standard deviations in 354 Asian and 317 African males in the three age-groups selected for study are summarised in table I.

The slight difference in mean value between the 12-year and 20-year Asian groups is not statistically significant, but there is a substantial difference in mean value between these levels and those seen in the over-40 group. The Asian results at 20 and over 40 years are very similar to those found in American men in Minnesota by Keys and Keys (1954).

The mean serum-cholesterol levels in the 12-year and 20-year African groups are almost identical, despite the fact that the former group represents predominantly one local tribe while the latter is composed of tribes from all over East Africa. In the adult African group the mean level falls to 144 mg. per 100 ml.; and, as these subjects were unselected, the possibility of there being a chance predominance of one or other socioeconomic group was considered. The subjects were grouped by tribes, there being 61 Baganda, 22 Ruanda, and 37 from other tribes with mean serum-cholesterol concentrations of 152, 124, and 144 mg. per 100 ml. respectively. Even if the Baganda alone were considered, as representing the highest socio-economic group of the three, there would be no rise in mean concentration with age, such as is seen in those communities susceptible to coronary heart-disease (Keys and Keys 1954). The mean levels when grouped by tribes suggest a definite correlation with the socioeconomic position in the community.

TABLE II—MEAN SERUM-CHOLESTEROL CONCENTRATIONS IN ASIAN VEGETARIANS AND NON-VEGETARIANS IN KAMPALA, UGANDA

Age (yr.)	Serum-cholesterol (mg. per 100 ml.) (mean & S.D.)	
	Vegetarian	Non-vegetarian
12-year and 20-year groups	(47) 209 ± 50	(177) 209 ± 47
Over-40 groups ..	(93) 236 ± 46	(37) 274 ± 52

Numbers in parentheses are numbers of subjects in each group.

As pure vegetarians have been shown to have considerably lower serum-cholesterol levels than non-vegetarians (Hardinge and Stare 1954), we analysed the results to determine whether the vegetarians and non-vegetarians in the Asian community displayed differences (table II). In point of fact, many who professed pure vegetarianism were found to be lacto-ovo-vegetarians, and many took meat on occasion. Whatever the dietary group, food was prepared with the same fats and oils—i.e., cottonseed oil and ghee.

Discussion

The mean serum-cholesterol levels of Africans and Asians differed considerably at all the ages studied. Thus any factor or factors responsible for this difference must be present and effective at all three ages, and in the reasons for this interracial difference may be found the factors responsible for the differing racial susceptibility to coronary heart-disease. Climatic and geographic environmental factors are the same in the two groups, and Bronte-Stewart et al. (1955) have emphasised the considerable overlap from race to race despite interracial differences in mean values.

Physical activity, as suggested by Mann et al. (1955), cannot be held responsible for the difference in the mean serum-cholesterol levels of young Africans and Asians—schoolchildren and students. Moreover, Keys et al. (1956) think that differences in physical exertion cannot explain the large differences found when groups of people with different dietary habits are studied. Though work entailing physical activity may be protective against coronary heart-disease (Morris and Crawford 1958), it cannot *by itself* account for the differences in mean cholesterol levels seen in Western countries and the so-called primitive areas.

In South Africa Bersohn and Wayburne (1956) have demonstrated that African and European babies at birth have the same mean serum-cholesterol levels, despite significant differences in the mean levels in the African and European mothers. Sperry (1936) showed that in the first three to four days of life the total cholesterol content of the plasma increases—by an average of 76% in 15 subjects—but from the age of 4 to 25 days there was neither increase nor decrease. From the 2nd month to the 13th year the average cholesterol level in children, calculated for each year of age, does not change appreciably and is almost the same as that found in healthy adults aged 19–43 (Hodges et al. 1943). Studies in New York (Adlersberg et al. 1956) confirm that the serum-cholesterol levels in males remain constant from 2 to 19 years, after which there is a significant but gradual increase to the mid-30s. It seems likely, therefore, that for each community with its own specific nutritional background the characteristic " young adult " level is reached in the first few years of life, possibly because of the changeover to adult types of food. Our own findings in Kampala agree with this.

Various workers have differed somewhat in their reports on cholesterol levels from the mid-30s to the 6th decade. Some have found a gradual rise with age (Gertler et al. 1950, Keys et al. 1950, Lawry et al. 1957). On the other hand, Adlersberg et al. (1956), and Oliver and Boyd (1953) in Scotland showed no progressive rise in total cholesterol with age after 33, and a study by Keys (1952) on men in Naples with a low fat intake showed that a plateau was reached in the mid-30s. Thus a rise in serum-cholesterol does not necessarily accompany ageing.

Walker and Arvidsson (1954) demonstrated no significant rise with age in the South African urban Bantu, while Keys et al. (1958), in studies in Japan on men with an intake of less than 10% of total calories from fat, found only a moderate rise with increasing age. In South Africa Bronte-Stewart et al. (1955) reported a mean serum level of 166 mg. per 100 ml. in African men over 40, and, as in Uganda, this group experienced little or no coronary heart-disease. The implications of their findings is that the customary dietary habits of communities may be reflected in their mean serum-cholesterol levels and that increases in cholesterol level run strikingly parallel to increases in consumption of animal fats and a rise in income. This correlation between mean serum-cholesterol levels and socioeconomic standards has been demonstrated in West Africans (Edozien 1958), Johannesburg Bantu (Bloomberg et al. 1958), and Israelis (Brunner and Löbl 1957, Toor et al. 1957).

The African adults in this Kampala study, on a diet to which fat contributes some 10–15% of total calories, have a mean serum-cholesterol level roughly the same as that seen in the two younger age-groups. The Asian over-40 group, however, showed the progressive rise with age seen in other population groups with a high intake of fat. Keys and Keys (1954) maintain that in all areas where mean serum-cholesterol levels increase with age the diets have been shown to be relatively high in fat, which provides about 35 to 40% of the total calories. The Kampala Asian community, with a fat intake estimated at some 30–45% of total calories, provides further evidence that a rise of serum-cholesterol with age is associated with abundance of fat. Some of this fat is taken as unsaturated cottonseed oil, which might be expected to prevent a rise in serum-cholesterol. But our results show that the mere taking of unsaturated as well as saturated fat, without regard to the relative quantities, cannot achieve the results obtained under experimental conditions.

Our findings (table II) are the same as those noted by Hardinge and Stare (1954) in their nutritional studies on vegetarians. In young people there is presumably some physiological mechanism whereby, within certain limits of a fat intake, serum-cholesterol levels are maintained at or below about 200 mg. per 100 ml.; and with ageing or a decline in physical activity this mechanism may no longer cope with a heavy intake of fat. The higher cholesterol levels in the Kampala Asian non-vegetarian adults thus reflects their high intake of saturated fat.

The concept of an " ideal " level of serum-cholesterol has been raised—a concept which assumes an ætiological relation between the serum-cholesterol concentration and atherosclerosis. Bloomberg et al. (1958) regard the ideal value as 170–180 mg. per 100 ml., because they consider that the level of 150 mg. per 100 ml. (Lawry et al. 1957) is that found in primitive communities with a background of malnutrition. Our figures in African schoolboys and university students would support their contention that the ideal level is about 170 mg. per 100 ml., for neither of these two groups could be said to be malnourished, though their diets may be considered unsatisfactory as regards animal protein. The lower mean serum-cholesterol levels in the African over-40 group in Kampala may be an indication of relative malnutrition in this group, and certainly the tribal levels obtained support this view.

These observations on serum-cholesterol levels in different parts of the world are consistent with the hypothesis that the level of blood-lipids is artificially raised in " successful " modern civilisations (*Lancet* 1957) and that this appears to be an essential condition for coronary heart-disease to become endemic in a people. While a rise of blood-lipids does not cause thrombosis, it undoubtedly predisposes to it.

Summary

A study was made of the dietary background and serum-cholesterol levels in African and Asian males aged 12 years, 20 years, and over 40 years in Kampala, Uganda. These two racial groups differ markedly in their liability to coronary heart-disease.

At all three ages Africans and Asians show a considerable difference in the mean level of serum-cholesterol. This corresponds to their different consumption of fat.

The results of this survey support the view that a rise in serum-cholesterol level is not a necessary accompaniment of ageing.

If an ætiological relationship does exist between coronary heart-disease and the serum-cholesterol concentration, a level of 170 mg. per 100 ml. is suggested as "ideal".

We wish to acknowledge the contribution of Miss J. Summerscales, biochemist, Uganda Medical Service, for her work on one of the African groups. We are grateful to Prof. A. W. Williams for his encouragement and to Dr. R. F. A. Dean for his helpful criticism during the preparation of this paper. We are grateful to the headmasters of the several schools concerned and to the general practitioners, without whose cooperation this work could not have been completed. One of us (A. G. S.) is in receipt of a research grant from the Makerere College grants committee.

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THE IN-VITRO UPTAKE OF ^{32}P BY RED BLOOD-CELLS IN THYROID DISEASE

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THE effects of thyroid hormone are not easily measured, except by determination of the basal metabolic-rate. Searching for new indices of the action of thyroxine, Ermans and Bastenie (1957) measured the rate at which radioactive phosphorus (^{32}P) disappeared from the blood after the injection of red blood-cells labelled with ^{32}P. The isotope left the cells rapidly in thyrotoxic subjects, and slowly in myxœdematous subjects. But the technique is relatively complex and time-consuming because the patient has to have a series of venepunctures over a period of 72 hours.

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The uptake of ^{32}P by red blood-cells can be studied in vitro under simple conditions (Prankerd and Altman 1954). Such a method should be applicable as an index of thyroxine action if the rate of ^{32}P uptake by red blood-cells was proportional to the rate of discharge. We therefore incubated ^{32}P in blood drawn from normal subjects and from patients with thyroid disease. The rate at which the ^{32}P entered the blood-cells in vitro was calculated from serial measurements of the amount of ^{32}P remaining in the plasma at different times, and from the hæmatocrit. We here describe our technique and the results.

Method

^{32}P was supplied by the Radiochemical Centre, Amersham, as orthophosphate in isotonic solution containing 1 mg. per ml. of phosphate buffer at pH 7, and with a radioactivity of about 1 mC per ml. This solution was diluted with sterile isotonic saline to give an activity of about 10 μC per ml., and sufficient was used for each test to give an activity of 0·4 μC.

For each test about 15 ml. of venous blood was taken and transferred immediately to a heparinised bottle. As soon as possible 2 ml. of blood was removed for measuring the hæmatocrit in duplicate, and the remainder was poured into a test-tube containing 0·4 μC of ^{32}P. After gentle shaking to allow even mixing of the isotope, the test-tube was placed in a water-bath at a constant temperature of 37°C. A mixture of 95% oxygen and 5% carbon dioxide was bubbled slowly through the blood throughout the period of incubation.

For the first series of tests four samples, each of 2–3 ml., were removed at intervals of 20–30 minutes. Each sample was centrifuged immediately at 2500 r.p.m. for 5 minutes. 1 ml. of plasma was then removed and diluted with a carrier solution of NaH_2PO_4 to a final volume of 10 ml. In addition, 1 ml. of blood was withdrawn from the test-tube during incubation, and was completely hæmolysed by adding 9 ml. of a solution of NaCl and NaH_2PO_4 together with a few grains of saponin. The radioactivity of each sample was then measured in a M.6 liquid counter. After the validity of the method had been established, the technique was modified so that only two samples of blood were taken—the first 40–50 minutes, and the second about 75 minutes, after the addition of ^{32}P to the blood. 1 ml. of whole blood from each sample was hæmolysed and counted, and 1 ml. of plasma from each sample was counted after separation from the red cells.

Calculation

We thought that the rate of ^{32}P uptake by the red blood-cells would be a suitable parameter to use for our investi-

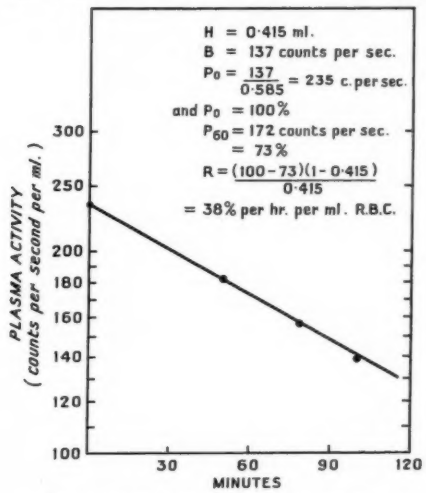

Fig. 1—Method of calculation of results.

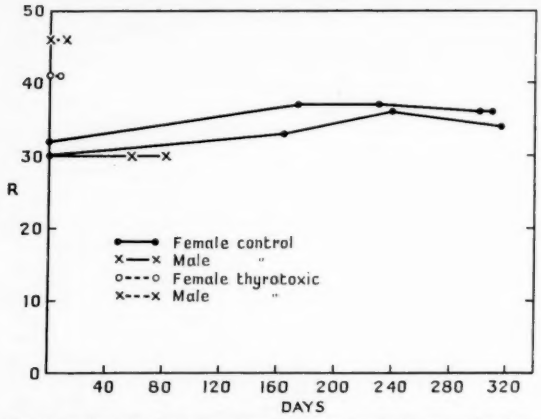

Fig. 2—Values for R during repeated tests on three normal volunteers and two thyrotoxic patients.

gation. This was calculated for each case and expressed as " R ", being the percentage of the available activity per millilitre of blood taken up by each millilitre of red cells per hour.

The total activity (B) in each ml. of blood, which remains constant throughout the experiment, was measured in the samples of completely hæmolysed whole blood. The activity in 1 ml. of plasma (P) at various times during incubation was measured in the serial plasma samples. The activity (R) in the red cells at any time can be calculated from the formula:

$$B=P(1-H)+RH$$

where H, the volume of cells in 1 ml. of blood, is obtained by measuring the hæmatocrit. At zero time (when the ^{32}P is added to the blood) it is assumed that all activity will be in the plasma, and that R=O, so that:

$$B=P_0(1-H)$$

and the first equation can be rewritten as:

$$P(1-H)+RH=P_0(1-H)$$

$$\text{or } R=\frac{(P_0-P)\,(1-H)}{H}$$

For each experiment the value of R was calculated for 1 hour, and the relevant value of P (i.e., P_{60}) was taken from the graph.

Results

Our technique was similar in essentials to that devised by Prankerd and Altman (1954). We confirmed their findings that the blood remained at a constant pH for about 3 hours, after which the pH altered and hæmolysis occurred. Excessive aeration of the blood also caused hæmolysis. A wide-bore central tube allows gentle aeration without frothing, so that coating the glassware with silicone was found to be unnecessary as long as the pressure of the gas was kept low.

The exponential character of the decrease of activity in plasma with time is illustrated in fig. 1. When individual plasma samples did not conform to this exponential pattern there had usually been technical faults. In a very few cases, however, the rate of clearance from the plasma was not exponential, and repeated tests on the same patients showed the same non-linear results. No explanation could be found for this, but it happened slightly more often with the blood from hypothyroid subjects. The reproducibility of R is shown in fig. 2. Blood samples studied in duplicate under the same conditions gave identical values for R, but variations in temperature of more than 1°C affected the results. The best results were obtained if the blood was added to a warmed tube and incubated with the ^{32}P within 20 minutes of collection. An interval of more than one hour between taking the blood and its incubation was undesirable. The control of pH seemed to be important. Blood samples studied in duplicate at pH 3 and 7 gave widely different results.

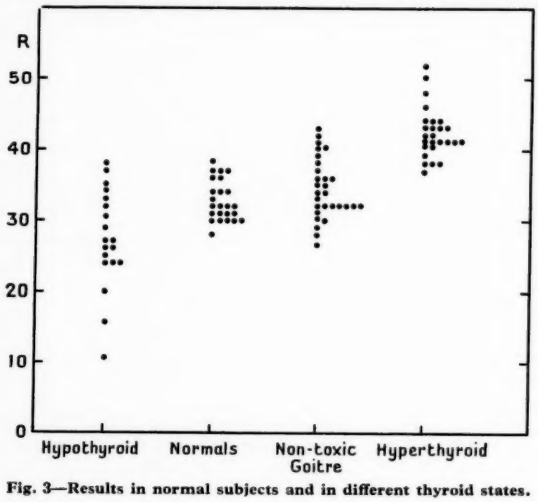

Fig. 3—Results in normal subjects and in different thyroid states.

TABLE I—CORRELATION OF R WITH DIFFERENT THYROID DISORDERS

Data	Test	Result	Significance
Correlation of R and S in cases with toxic or non-toxic goitre	r	$r=0{\cdot}52$	Highly significant ($P<0{\cdot}001$)
Values of R in toxic or non-toxic cases	t	$t=5{\cdot}923$ $n=57$	Highly significant ($P<0{\cdot}001$)
Values of R in non-toxic or hypothyroid cases	t	$t=3{\cdot}705$ $n=47$	Highly significant ($P<0{\cdot}001$)

TABLE II—VALUES FOR R WHEN THE RED CELLS AND PLASMA FROM TWO DIFFERENT SUBJECTS ARE " CROSS-MATCHED "

A plasma + A cells	A plasma + B cells	B plasma + B cells	B plasma + A cells
50	46	41	41
41	38	30	29
29	29	31	30
36	36	33	32·5
34	33	33	32
33	33	36·5	32

The correlation of R with different thyroid disorders is shown in table I. In forty-one thyrotoxic and euthyroid patients the rate of uptake of radioactive iodine (^{131}I) was measured during the first half-hour after intravenous injection; this index of thyroid function was expressed by " S " (Farran 1958). The correlation between S and R was found to be statistically highly significant ($P<0{\cdot}001$).

A small investigation was carried out to investigate whether the rate of uptake of ^{32}P by the red cells was regulated by factors in the plasma or in the cells. The values of R were accordingly determined for red cells from patients with abnormal thyroid function incubated with plasma from normal subjects, and vice versa. The preliminary results suggest that the value of R so obtained depended on the plasma and not on the cells (table II). More data is being collected on this subject.

Other possible causes of variation were studied, particularly the effect of abnormal hæmatocrits which did not affect the value of R. The presence of cardiac disorders, however, tended to lower the value of R, even in euthyroid patients.

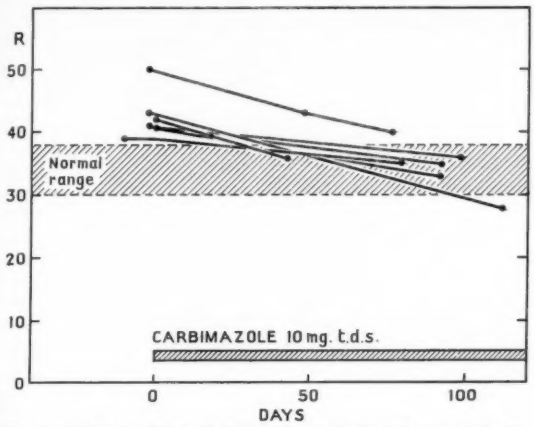

Fig. 4—Values for R in six thyrotoxic patients before and during treatment with carbimazole.

In-vivo techniques have the advantage that the patient does not receive any radiation.

Discussion

Ermans (1958) measured the rate of disappearance of ^{32}P from the red blood-cells, in vivo, 15–55 hours after the injection of cells which had been labelled with ^{32}P. He reported a definite separation between groups of hypothyroid, euthyroid, and hyperthyroid patients, with only very slight overlap between the euthyroid and hyperthyroid groups. With our in-vitro test the distinction is not so clear, and there is considerable overlap between each group (fig. 3). The correlation of R with the clinical diagnosis was found to be statistically significant, however, P being $<0{\cdot}001$ for each group. Neverthless the value of R as a diagnostic test is limited, although the change in R for any individual patient seems to be an accurate measure of the variations in the thyroid state.

Clinical study of the patients in whom the results were anomalous showed that there are conditions in which the test is not specific for thyroid function. We found abnormally high values in patients who were being treated with large doses of cortisone or its analogues. In certain cardiac disorders the results were in the lower range of normal and in the hypothyroid range.

Measurements involving ^{131}I are invalidated by the use of thyroid or of anti-thyroid drugs. Hence tests based on the use of ^{131}I are useless for weeks or even months after

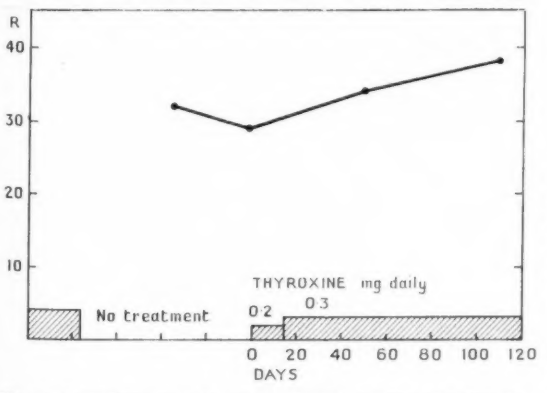

Fig. 5—Variations in R in a hypothyroid patient, showing the increase in the value of R when treatment was started again.

such forms of therapy, whereas the patient's response to treatment or to its withdrawal can be followed accurately by repeated measurement of the rate of uptake of ^{32}P by the red cells.

Serial measurements of ^{32}P uptake by red cells provide a reliable guide to the patient's thyroid status during treatment for thyrotoxicosis or myxœdema. Fig. 4 shows the values for R in patients before and during treatment with carbimazole in doses of 10 mg. t.d.s., while fig. 5 shows the response of a patient to treatment with *l*-thyroxine. The test is of particular value under those conditions which invalidate ^{131}I techniques.

Summary

A relatively simple technique is described for measuring in vitro the rate of uptake of radioactive phosphorus (^{32}P) by the red cells, and the results in a hundred patients are discussed.

The ^{32}P was taken up rapidly in thyrotoxic subjects, and slowly in myxœdematous subjects.

This technique can be used during or immediately after stopping treatment with anti-thyroid drugs or with thyroid, and it has the advantage that the patient does not receive any radiation.

We should like to thank Dr. D. F. Rideout for his valuable assistance, and Dr. A. J. Lea for much helpful advice and assistance with the statistics.

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COE VIRUS
PROPERTIES AND PREVALENCE IN GREAT BRITAIN

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DURING laboratory investigations connected with a trial of adenovirus vaccine at Royal Air Force recruit stations early in 1958, four strains of an agent with a cytopathic action on HeLa-cell cultures were isolated. This agent had some properties of enteroviruses, but could not be identified with known members of this group. It proved identical with an agent, named Coe virus by Lennette et al. (1958), isolated from military recruits in California. Its prevalence in this country was investigated by a serological survey.

Materials and Methods

Pathological Specimens

Throat-swabs from patients with acute respiratory illness were sent suspended in 2 ml. of Hanks' balanced salt solution and stored at −70°C until tested. Human sera examined in the serological survey were received for miscellaneous laboratory investigations. Forty-six of the sera from children under 10 years of age were taken about 2 weeks after the onset of the acute respiratory illness which necessitated admission to hospital.

Virus Strains

Coe virus propagated in HeLa-cell cultures was kindly sent by Dr. Lennette (California State Department of Public Health, Berkeley, California). Of the four strains isolated by us, one named 095 was used in most of the experiments here reported.

Antisera

A serum from a monkey hyperimmunised with Coe virus was also received from Dr. Lennette. Antiserum against the 095 strain was obtained from rabbits inoculated with HeLa-cell culture material given intravenously in 1 ml. amounts weekly for 4 weeks and bled 10 days after the last inoculation. The serum was inactivated at 56°C for half an hour and kept stored at −30°C.

Tissue Cultures

HeLa cells were propagated and maintained by methods previously described (Pereira and Kelly 1957). For detailed cytological studies HeLa cells were grown in tubes containing coverslips measuring 7×22 mm. on to which the cells were allowed to settle. Coverslips from infected and non-infected cultures were fixed in absolute alcohol at room temperature and stained with hæmatoxylin and eosin.

For the plaque technique, petri-dish cultures of HeLa cells were inoculated with 1 ml. volumes of virus dilutions, allowed to absorb for 1 hour, washed, and layered with a maintenance medium containing 5% rabbit serum, 0·25% lactalbumin hydrolysate (L.A.H.), 0·8% agar, and 1/10,000 neutral red, and incubated in an atmosphere of 5% CO_2.

Monkey-kidney cultures were prepared and maintained as described elsewhere (Pereira 1958).

Cultures of human amnion were maintained in Gey's solution with 0·25% L.A.H. and 10% calf serum.

Cultures of the E.R.K. line of rabbit kidney (Westwood et al. 1957) were maintained in Gey's solution with 0·25% L.A.H. and 5% rabbit serum. All tissue-culture media contained 100 units penicillin, and 100 μg. streptomycin, per ml.

Infectivity Titrations

Virus preparations were diluted in tenfold steps in Gey's solution and 0·1 ml. of each dilution was inoculated into each of four HeLa-cell cultures. Cultures were examined for cytopathic effects and the 50% infectivity end-point was read after 5 days' incubation.

Serum Neutralisation Tests

Sera were diluted in Gey's solution in twofold steps. 100 I.D.$_{50}$ of virus were added to each dilution and the mixtures kept at room temperature for 1 hour. Each mixture was then inoculated into two tubes of HeLa cells. Neutralisation end-points were read at 5 days. For the serological survey, each serum was tested at a dilution of 1/10.

Results

Virus Isolations

The four patients from whom virus was isolated had pyrexia (not exceeding 99·6°F), pharyngitis, and cough. Other symptoms included coryza (3), cervical adenitis (3), hoarseness (2), mild conjunctivitis (3), headache (2), and chest and muscle pains (1). The diagnosis reached by the clinical observers was febrile cold in two cases, febrile sore throat in one case, and influenza in one case. All patients were admitted to hospital but made rapid and uneventful recoveries.

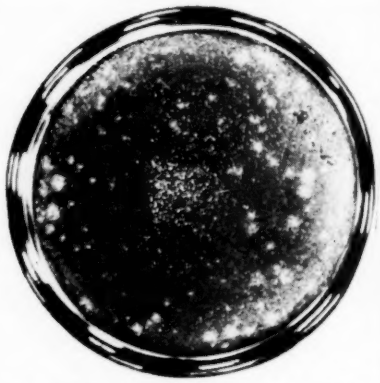


Fig. 2—HeLa-cell culture showing plaques caused by 095 virus.

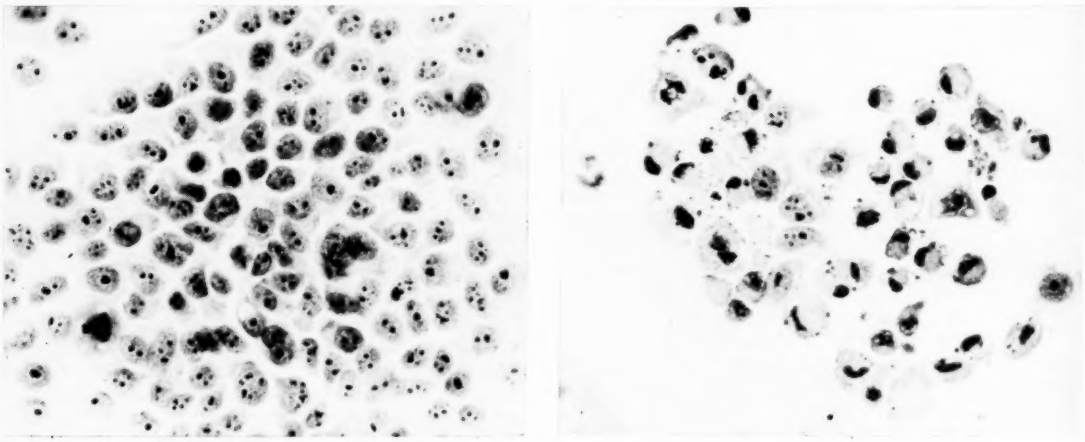
HeLa-cell cultures inoculated with throat-swab material from these patients showed degeneration starting between the 10th and 16th day of incubation. The virus was propagated serially in HeLa cells, reaching infectivity titres of the order of 10^5–10^7 in culture fluids. These fluids did not agglutinate fowl, guineapig, human O, or sheep erythrocytes at 4°C, room temperature, or 37°C.

Properties of Strain 095

The cytopathic effect of strain 095 in HeLa cells (fig. 1) consisted of a shrinking and rounding of cells followed by their detachment from the wall of the tube. Infected cells examined after staining with hæmatoxylin and eosin showed nuclear alterations consisting of coarsening and margination of the chromatin followed by nuclear pyknosis. A large mass of cytoplasmic eosinophilic material was often seen causing compression of the nucleus, which assumed a crescentic shape.

Inoculation of HeLa cells by the technique of Dulbecco and Vogt (1954) produced typical plaques (fig. 2) appearing after 3 days' incubation and reaching their maximum number 2 days later. A plot of the number of plaques against virus dilution gave a linear relation suggesting that each plaque was initiated by a single virus particle. Virus material titrated by both the plaque technique and the ordinary tube infectivity test gave titres of $10^{6·8}$ plaque-forming units per ml. and $10^{7·7}$ 50% infective doses per ml.

The virus could also be propagated in cultures of human amnion and a cell line of embryonic rabbit kidney (E.R.K.) and in both it caused cellular degeneration. No cytopathic effect



(a) (b)

Fig. 1—(a) Normal HeLa cells (×340). (b) HeLa cells 24 hours after inoculation with 10_4 I.D.$_{50}$ of strain 095 (×340).

TABLE I—FILTRATION OF STRAIN 095 THROUGH GRADOCOL MEMBRANES

Average pore diameter	T.C.D.$_{50}$ per ml. of filtrate
700 mμ	$10^{7\cdot7}$
260 mμ	$10^{7\cdot5}$
110 mμ	$10^{6\cdot7}$
53 mμ	$10^{3\cdot5}$
28 mμ	$<10^{1\cdot0}$

or evidence of multiplication was obtained in monkey-kidney cultures.

Intracerebral and intraperitoneal inoculation into suckling mice caused paralysis in occasional animals about the 8th day after inoculation. Attempts to propagate the virus by serial passages in further litters were unsuccessful and no virus could be recovered from brain or other tissues of the paralysed mice. No evidence of infection could be detected in adult mice inoculated by the intracerebral or intraperitoneal routes.

10-day-old fertile hens' eggs inoculated with strain 095 by the amniotic, allantoic, and chorioallantoic routes showed no sign of infection. The amniotic and allantoic fluids were tested for hæmagglutinins with fowl and guineapig cells at 4°C and at room temperature with negative results.

The sensitivity of the 095 strain to ether treatment was tested by adding 20% ether to infected tissue-culture fluid and leaving this for 2 hours at 4°C. There was no measurable loss of infectivity. The size of the virus was estimated by filtration through gradocol membranes (Elford 1931). Results are shown in table I and are consistent with a virus diameter of about 20 μ.

A comparison of strain 095 with Coe virus was made by means of serum neutralisation tests. The two strains gave identical neutralisation end-points with 095 antiserum (titre 1/640) and with Coe antiserum (titre 1/2560). The other three strains isolated at the same time as strain 095 also proved to be identical when tested by serum neutralisation with 095 antiserum. Strain 095 was tested by serum neutralisation with antisera for poliovirus types 1–3, Coxsackie B 1–5 and A9, and ECHO 1–14. All gave negative results.

TABLE II—PROPORTION OF SERA SHOWING ANTIBODY TO COE VIRUS IN DIFFERENT AGE-GROUPS

Age	Males			Females		
	Antibody		% positive	Antibody		% positive
	+	−		+	−	
0–10	0	39	0	1	39	2
11–20	4	16	20	2	17	11
21–30	9	13	41	2	26	7
31–40	11	11	50	2	15	12
41–50	4	6	40	3	9	25
51–60	13	8	62	6	4	60
61–70	15	6	71	11	10	52
Total	56	99	36·1	27	120	18·4

Antibody Survey

The presence of antibodies to strain 095 in sera of different age-groups and according to sex was investigated by serum neutralisation. The results (table II) show that the proportion of sera with antibodies to strain 095 increases with age, being relatively low in childhood. The frequency of positive sera was significantly higher in males. This difference was evident at all ages in which there was a sufficient number of positive sera. The significance of the difference for the whole group was estimated by χ^2, which gave a value of 11·9 ($P = <0{\cdot}001$).

It should be noted that in the age-group 0–10 years forty-six sera were from children convalescing from acute respiratory infections. No evidence of infection with Coe virus was obtained in any of the sera of this selected group.

Discussion

Several agents belonging to the enterovirus group have been isolated in monkey-kidney cultures from cases of upper respiratory disease (see review by Andrewes 1959). The Coe virus differs from these in that it was readily isolated in HeLa-cell cultures and failed to grow in monkey-kidney cultures.

A similar agent was isolated by Kasel et al. (1958) from the stools but not the respiratory secretions of eight patients with respiratory disease. These strains, however, were not pathogenic for suckling mice.

An enterovirus named 57–67 was isolated by Fukumi et al. (1957) in HeLa-cell cultures from throat washings of a child with respiratory symptoms. This virus was also non-pathogenic for suckling mice and was later shown (Fukumi et al. 1958) to be antigenically related to ECHO 6 and ECHO 1 viruses.

The findings on the properties studied in the present investigation—namely, size, ether resistance, and type of cytopathic effect—support the suggestion that the Coe virus should be included among the enteroviruses. It is, however, unrelated to other members of the group.

The results of our serological survey indicate a low rate of infection among children in Great Britain. This is in contrast to the findings of Fukumi et al. (1958) with the 57–67 virus in Japan. They found antibodies in 50% of children by the age of 3 years. The reason for the greater incidence of antibodies among males is not clear, but military training may give more opportunity for infection. This possibility is supported by the results of a survey of respiratory infection at two R.A.F. recruit stations during 1958–59 (to be published). Numerous strains of Coe virus have been isolated from patients who afterwards showed antibody rises to the same agent. This fact suggests epidemiological similarity with adenoviruses types 4 and 7.

Summary

Virus isolated from four patients with respiratory disease was identified as Coe virus by serum neutralisation tests. Its inclusion in the enterovirus group is supported by its size, ether resistance, and type of cytopathic effect.

A serological survey indicated that the incidence of infection with the virus in Great Britain is low in children and rises steadily with age; and that antibodies are commoner in males, especially among young adults.

We wish to thank the M.R.C. Committee on Influenza and Other Respiratory Vaccines, and the Directorate of Hygiene and Research of the Royal Air Force for permitting us to use records and specimens; also Dr. E. H. Lennette for sending us the Coe virus and antiserum, Dr. C. C. Spicer for help with the statistical analysis, and Mr. R. Jay and Miss A. Deacon for technical assistance.

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". . . We are all sanitarians—some of us more fortunately situated than others. Perhaps we bask at our ease in the complex pipeline civilisation of the western world, not forgetting of course the as yet often unmitigated pollution of the atmosphere which is such an unnecessary concomitant of industrial effort. Perhaps, on the other hand, we are engaged upon a continuing and only slowly successful battle with nature. Yet the principles of our training and practice are the same. We know that the healthy environment, expensive though it may be to obtain, and slow to be achieved, is an essential component of healthy living."—Sir JOHN CHARLES, F.R.C.P., *WHO Chron.*, July-Aug. 1959, p. 297.

AORTITIS IN CHILDREN

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IN the past two years four children have been admitted to Baragwanath Hospital in congestive cardiac failure with hypertension, and an unusual arteritis of the aorta has been found post mortem. Another child whom we have had under observation for about a year, with hypertension and evidence of a dilated aorta, is thought to have the same condition.

Two cases will be briefly reported here.

Case-reports

FIRST CASE

An African girl aged 9 years was admitted to the hospital on Aug. 20, 1958, in congestive cardiac failure. She had had a cough and progressive breathlessness for 2 weeks, and for 2 days there had been swelling of the legs and feet and vomiting. She had seven healthy siblings, and until the onset of these symptoms had eaten well and developed normally.

She was an extremely dyspnœic, distressed child weighing 42½ lb. Her temperature was 98·6°F, pulse-rate 142, and respiratory rate 84. The blood-pressure in the right arm was 150/120 mm. Hg. The jugular venous pressure was raised 7 cm. and the liver edge was 6 cm. below the right costal margin.

The cardiac impulse was heaving and situated in the sixth left intercostal space 1·5 cm. beyond the midclavicular line. A right ventricular tap was also felt. There was a gallop rhythm over the apex, and along the left sternal border up to the second left intercostal space. A grade-II systolic murmur was heard to the left of the sternum in the second and third intercostal spaces. The lungs were clinically clear. The femoral pulses were absent. The systolic blood-pressure in the lower limbs varied from 90 to 100 mm. Hg. There was no cyanosis and no obvious œdema of the sacrum or lower limbs, and the extremities were cold. The urine contained albumin (++), but a centrifuged specimen showed only uric-acid crystals, scanty red cells, and occasional polymorphs. Electrocardiography confirmed a large left ventricle.

Course of Illness

A diagnosis of coarctation of the aorta with congestive cardiac failure was made. The child was propped up in an oxygen tent, sedated and digitalised, and placed on a salt-free diet. Next day there was slight improvement, and radiological examination showed a grossly enlarged heart and congested lung fields. No rib notching was seen.

2 days after admission the temperature rose to 102°F, but the pulse-rate had slowed. No cause could be found for the pyrexia. There was still a grade-II systolic murmur over the left second and third intercostal spaces, but in addition a diastolic murmur over the same areas was also heard. The urine contained no red cells, and there was no splenomegaly. Diagnoses considered were subacute bacterial endocarditis, a patent ductus arteriosus, and an incompetent bicuspid aortic valve.

Examination of the blood showed a hæmoglobin of 13·4 g. per 100 ml. and white cells 14,800 per c.mm. (68% polymorphs, 29% lymphocytes, 2% monocytes, and 1% eosinophils). The erythrocyte-sedimentation rate was 9 mm. (Wintrobe). The blood-urea was 78 mg. per 100 ml., and serological tests for syphilis were negative.

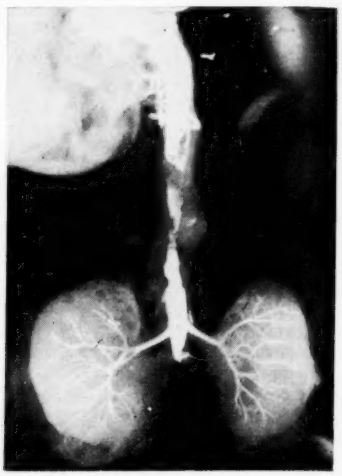

Fig. 1—Postmortem radiograph showing segmental partial occlusion of the aorta.

The child improved on intramuscular penicillin and remained more or less apyrexial. The initial clinical improvement on rest and digitalis continued, and the thoracic surgeons were willing to undertake a resection of the stenosed aorta when the child was fit enough.

However, 34 days after admission she suddenly deteriorated. On further digitalisation and diuretics she again improved, but after a few days her condition worsened and she developed œdema of the sacrum and legs. She died 75 days after admission.

Postmortem Findings

Necropsy.—The heart weighed 220 g., with considerable left ventricular hypertrophy. The valves were all normal. Postmortem radiographic studies showed partial occlusion of the aorta from 6 cm. distal to the origin of the left subclavian artery to about 2·5 cm. proximal to the origin of the cœliac artery (fig. 1). A cross-section of the aorta showed a large thrombus filling the lumen. The ascending aorta and arch were mildly atheromatous, but distal to the renal arteries the intima was healthy. There was no evidence of a congenital coarctation of the aorta.

Histologically the aorta showed partial organisation and recanalisation of the occluding thrombus (fig. 2). This was evidently of some standing, for its organisation had in parts produced marked fibrous intimal thickening. The adventitia showed fibrosis and a dense perivascular lymphocytic infiltrate. Many of the vasa vasorum showed an endarteritis, and several were partially occluded by recanalised thrombi. The inflammatory infiltrate extended into the media and was associated with focal granulation-tissue proliferation, with destruction of the elastica and muscle of the media (fig. 3). In several areas the inflammatory process involved the intima and

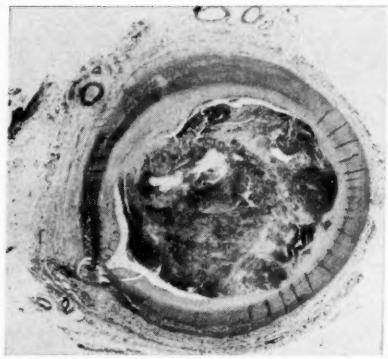

Fig. 2—Organised thrombus in the lumen of the aorta.
Note the occluded vasa vasorum at top left. (Hæmatoxylin and eosin. ×5.)

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Fig. 3—Inflammatory infiltrate invading the media.
There is capillary proliferation, and destruction of elastica and muscle. The thickened intima is seen above. (Hæmatoxylin and eosin. × 90.)

at one point pierced the internal elastic lamina. Proximal to the thrombus the inflammation was confined to the adventitia. Stains for spirochætes, acid-fast bacilli, fungi, and inclusion bodies were negative. Section of the great vessels revealed no abnormality.

The heart showed hypertrophy of the muscle bundles of the left ventricle. There was no evidence of rheumatic carditis.

SECOND CASE

Another African girl, aged 8, was admitted on June 10, 1957. She had had cough and increasing breathlessness for a month and chest pains for a week, and her feet had been swollen for a day. She had been quite healthy until a year previously, when she was admitted to another hospital with " sore eyes and a rash ". She suffered from occasional sore throats, and 5 months previously she had complained of painful wrists and knees.

She was a thin, dyspnœic child in congestive cardiac failure. The heart was enlarged with a heaving left ventricular impulse. The right radial pulse was bounding, and the blood-pressure in the right arm was 170/90 mm. Hg.

The pulses in the left upper limb could not be felt, but hard cord-like brachial and radial vessels were palpable. Nevertheless her hands were equally warm. On two subsequent occasions, slight pulsation was felt in the left radial artery but the blood-pressure was unobtainable in the left arm.

The right common carotid artery pulsated strongly. Pulsation over the left common carotid artery was decreased up to the bifurcation, where an expansile impulse was visible and a definite systolic thrill and murmur were present. Clinically, an aneurysm of the left common carotid artery was diagnosed.

All pulses in the lower limbs were full; the blood-pressure in both thighs was 170/120 mm. Hg. Radiography and electrocardiography confirmed an enlarged heart with left ventricular hypertrophy.

The urine contained protein (+++), and a centrifuged specimen showed a few hyaline casts and one to two polymorphs and red cells per high-power field. The hæmoglobin was 11·9 g. per 100 ml. The white-cell count was 10,200 per c.mm. with a normal differential count. The erythrocyte-sedimentation rate (Wintrobe) was 7 mm., and C-reactive proteins were increased (+++). Serological tests for syphilis were negative, and lupus-erythematosus cells were not found in the blood. The streptococcal antihæmolysin-O titre was 1600 units per ml.

The congestive failure was treated with digoxin and diuretics, but she died 5 days after admission.

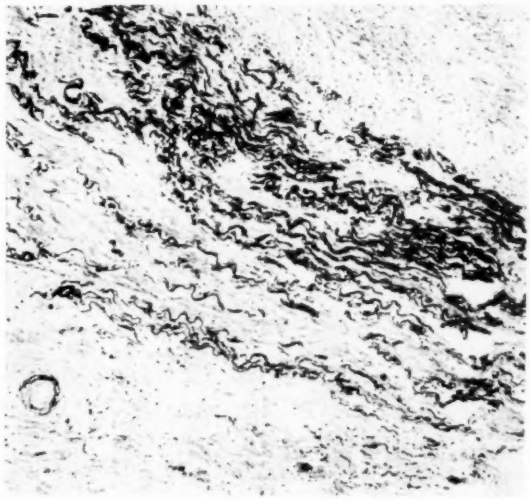

Fig. 4—Photomicrograph of the aorta.
Note the interruption of the elastic fibres of the media, fibrosis of the adventitia, and thickening of the intima. A vessel in the adventitia shows well-marked endarteritis. (Elastic-Masson. × 90.)

Postmortem Findings

Necropsy.—The heart (150 g.) was enlarged, mainly through left ventricular hypertrophy. Antemortem thrombi were found at the apex of the left ventricle and in the left atrial appendage. The valves were normal and the coronary arteries healthy.

Both lungs showed infarcts, and the pulmonary arteries contained antemortem thrombi. The pulmonary arteries showed some loss of elasticity, with focal areas of wrinkling of the intima.

There was moderate generalised fusiform dilatation of the arch and the first part of the ascending aorta. From 3 cm. distal to its origin to the origin of the renal arteries there was well-marked fibrous thickening of the wall with loss of elasticity. The intimal surface was opaque, swollen, and lustreless and in parts was pink. The affected segment of the aorta was

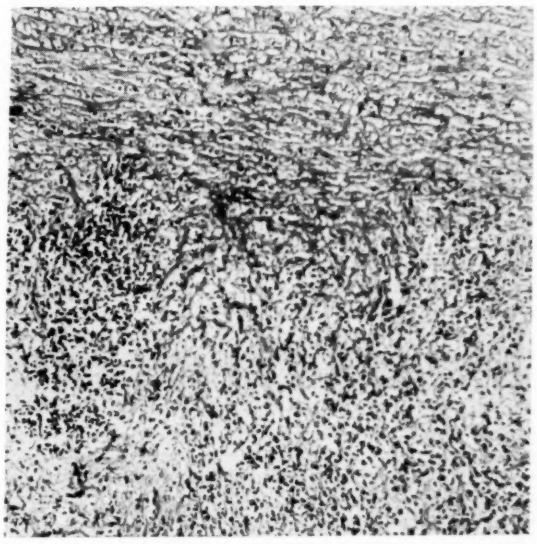

Fig. 5—Cellular infiltrate in the adventitia spreading into the media.
(Hæmatoxylin and eosin. · 100.)

raised 1·5 mm. above the level of the normal intimal surface. Distal to the origin of the renal arteries the aorta appeared normal. The adventitia over the affected area was thickened and there were several foci of intimal thrombosis. There was narrowing of the origins of the left subclavian, left vertebral, and right renal arteries. The left kidney was supplied by two arteries and the superior one was stenosed. The left common carotid artery showed periadventitial fibrosis with narrowing of the lumen up to the bifurcation. The iliac, axillary, brachial, and femoral vessels were normal.

The left kidney (105 g.) was larger than the right (70 g.), which showed large areas of cortical atrophy.

Histological examination.—The affected segments of aorta, the left common carotid artery, and the left subclavian artery showed fibrosis and vascularisation of the media with destruction of the muscle and elastica (fig. 4). There was focal and diffuse infiltration of the media and adventitia by lymphocytes, histiocytes, plasma cells, and polymorphs (fig. 5). The intima showed fibrous thickening. Occasional granulomata composed of irregularly arranged fibroblastic cells were found in the adventitia. The vasa vasorum showed endarteritis with perivascular cuffing. Antemortem thrombus was seen on the intima. Stains for spirochætes, fungi, acid-fast bacilli, and inclusion bodies were negative.

Sections of the heart showed myocardial hypertrophy and antemortem thrombi in the apex of the left ventricle, and in the left atrium. There was no evidence of a rheumatic carditis.

The lungs showed large hæmorrhagic infarcts with antemortem thrombi in the radicles of the pulmonary arteries. The walls of the vessels, however, were normal.

Discussion

The pathological findings in these two cases are very similar, consisting essentially of a severe arteritis of the aorta. In case 2 the arteritis also involved the great vessels arising from the arch of the aorta. The clinical features of case 2 conform in many respects with those reported in " pulseless disease ".

This arteritis of young females occurs typically between the ages of 15 and 40, although the disease has been described in males as well as in younger and older women. Necropsies have shown varying distribution of the lesions. Many have shown involvement of the subclavian and carotid arteries, starting close to their origin from the aorta without the latter being involved. In some, the aortic arch has been involved, obstructing the orifices of the carotid and subclavian arteries, and sometimes extending down to the abdominal aorta and involving the cœliac and mesenteric arteries (Harbitz 1926, Frövig and Löken 1951). The subject has been well reviewed by Koszewski (1958). Recently Lessoff and Glynn (1959) pointed out that the pulseless syndrome may be due to a variety of causes.

The histological findings in pulseless disease are very similar to those in our two patients—namely, a panarteritis with infiltration of the adventitia by lymphocytes and plasma cells, disruption of the muscle and elastica of the media, and fibrous thickening of the intima often with superimposed thrombosis. A similar histological picture was described by Gilmour (1941) in cases of what he called giant-cell chronic arteritis, a term which he used synonymously with temporal arteritis. Reid (1957) also reported four cases of giant-cell arteritis of the aorta. Cooke et al. (1946) in a review of temporal arteritis described changes in the aorta, temporal, radial, subclavian, and various visceral arteries. Pathologically these cases again showed changes resembling those in our two patients. But this disease occurs chiefly in elderly people, and has never been described in children.

An aortitis sometimes develops in rheumatic fever (Klotz 1913), and in rheumatoid arthritis (Cruickshank 1958), with histological changes very similar to those in our cases. Although in case 2 there was a history of sore throats and joint pains and the anti-streptolysin-O titre was raised, neither case showed any pathological evidence of rheumatic fever. Occasionally aortitis has been described in Buerger's disease and in periarteritis nodosa, but both these conditions can be excluded here. So can syphilis.

Summary

In four African children who died from congestive cardiac failure associated with hypertension, aortitis was found post mortem. Two of these cases are reported.

The histological appearances are similar in many respects to those of " pulseless disease " and temporal (giant-cell) arteritis.

We should like to thank the Superintendent of Baragwanath Hospital for permission to use the case-records; Prof. B. J. P. Becker for his helpful advice; the Director of the South African Institute for Medical Research for facilities granted; and Mr. M. Ulrich of the photographic department of the South African Institute for Medical Research.

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DIHYDROHYDROXYCODEINONE PECTINATE

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THE pharmacology of dihydrohydroxycodeinone pectinate (' Proladone ', Crookes) was extensively investigated by Aubry et al. (1951a and b), Truchaud (1954), and Mandel (1954). Their findings indicate that the drug is a well-tolerated potent analgesic with long-continued action and a wide safety margin. More recently, clinical reports in this country by Belam (1957) and Boyd (1959) have confirmed these findings.

Trial

A simple clinical trial of dihydrohydroxycodeinone pectinate has been carried out at this hospital during the past twelve months, solely to determine its effectiveness as an analgesic for the relief of postoperative pain and to assess any advantages over other such analgesics in common use. It has been used following various major operative procedures including orthopædic, abdominal, and thoracic operations in patients varying from 6 to 89 years of age (see accompanying table).

Various anæsthetic techniques were used (intravenous pethidine excepted); but on no occasion was the drug administered until the patient had regained consciousness and had

DISTRIBUTION OF 600 CASES IN WHICH DIHYDROHYDROXYCODEINONE PECTINATE WAS ADMINISTERED

Nature of operation	No. of patients	Av. age of patients (yr.)
Major orthopædic ..	95	56
,, abdominal ..	210	62
,, gynæcological ..	140	50
,, thoracic	80	38
Bilat. adrenalectomy ..	17	56
Radical mastectomy ..	14	54
Prostatectomy	44	69
Total	600	..

complained of pain in the operative site, unrelieved by routine measures such as change to the lateral position, relief of pull on drainage tubes and dressings, or support by pillows. Patients included in the trial were observed for up to $10^1/_2$ hours in a specially equipped and staffed recovery ward and thereafter in the surgical wards. Blood-pressure and respiratory rate were estimated every 15 minutes. In addition, tidal volume was estimated in 52 cases both before and after administration of the drug.

Analgesic Effect

Of the 600 patients to whom the drug was administered 534 (89%) experienced relief of postoperative pain. Of the remaining 66, 35 were probably given an inadequate dose of the drug; this was early in the series and was due to inexperience in assessing the optimum dosage. The remaining 31 patients failed to obtain adequate relief from dihydrohydroxycodeinone pectinate and were relieved by either morphine or pethidine.

The analgesic effect began 20–25 minutes following intramuscular injection and lasted for a remarkably long period, averaging 9 hours. The shortest effective period of analgesia was 5 hours and the longest 13 hours.

Dosage

10 mg. of the drug given intramuscularly was an effective dose for the adult of average weight, and this dose was given to 66% of patients in the series. Clinically 10 mg. dihydrohydroxycodeinone pectinate had an analgesic effect comparable to that of 10 mg. morphine or 100 mg. pethidine and was well tolerated even by ill and elderly patients. More robust patients, however, needed a larger dose, and in them 20 mg. was occasionally given. 5 mg. was an effective dose for children aged 6–12 years. With increased experience it has become our practice to give an initial dose of 10 mg. intramuscularly and, if necessary, an additional 5 mg. once or more during the next hour to obtain an optimum effect.

Tolerance

Side-effects were remarkably few. In about 70% of cases there was a mild hypnotic effect, often with a feeling of tranquillity and well-being, though not amounting to euphoria. Most patients tended to be drowsy and to sleep for varying periods. They were, however, easily rousable and their protective reflexes were not obtunded. This was noticeable where the drug had been given to patients who had undergone major thoracic surgery. Here it was quite easy to rouse the patient from sleep, stimulate him to cough, and then allow him to sleep again.

Nausea and vomiting were unusual, but as the trial of the drug was confined to the immediate postoperative period, when both anæsthesia and surgery are obvious contributing factors, it was decided to carry out a further survey of 100 patients to whom the drug had been given in the surgical wards after the first 48 postoperative hours. This showed an incidence of nausea and " dizziness " of 2% with no vomiting.

3 cases of known morphine intolerance, 1 of them severe, were included in the series. They all received dihydrohydroxycodeinone pectinate following operation and were quite free from nausea or any other side-effects. On several occasions dihydrohydroxycodeinone pectinate appeared to be effective where morphine or pethidine was either poorly tolerated or ineffective:

An obese, nervous woman, aged 59, underwent a lengthy operation for repair of a large hiatus hernia, followed by cholecystectomy and appendicectomy. Morphine 10 mg. given intramuscularly in the immediate postoperative period caused nausea, vomiting, and relief of pain lasting only $2^1/_2$ hours. She was then given pethidine 100 mg. This relieved the pain; but she became pale and shocked, perspiring profusely with severe peripheral vasoconstriction. 3 hours later she was again complaining of severe pain. She was given dihydrohydroxycodeinone pectinate 10 mg. followed in half an hour by a further 5 mg. and subsequently slept intermittently for 10 hours, apparently pain-free without nausea or other side-effects. Subsequent injections the following day relieved pain for 8–9 hours without any untoward symptoms.

Patients with liver dysfunction are often unduly susceptible to opiates. Aubry et al. (1951a) noted the absence of decreased tolerance in such patients to whom dihydrohydroxycodeinone pectinate had been given. Only 1 case in this series had severe liver damage:

A man, aged 49, developed jaundice due to cholangitis and multiple liver abscesses; he was in poor general condition and suffered severe pain. For 12 days he received dihydrohydroxycodeinone pectinate in doses of 10 mg. which effectively relieved his pain for 7–8 hours. In all, he received 230 mg. without symptoms of intolerance.

Routine recordings of blood-pressure and pulse-rate have shown how little the drug affects the cardiovascular system. In 40% of cases there was a transient fall in blood-pressure which appeared 40–60 minutes following intramuscular injection, but which was never greater than 10 mm. Hg except in 2 cases of overdosage (vide infra). In the remaining 60% of cases there was no change in blood-pressure attributable to the drug.

There appeared little or no respiratory depression where the 10 mg. dose was used even in poor-risk or elderly patients. The respiratory rate was either unchanged or reduced by 2–3 respirations per minute. Estimations in 52 cases of tidal volume, using the Draeger volumeter, confirmed the apparent absence of respiratory depression. In the more frail elderly patients, however, respiratory depression was seen on occasions where doses of over 10 mg. had been used. 2 instances of severe respiratory depression were seen. On each occasion a relative overdose (20 mg.) had been given to an elderly poor-risk patient, and in each case the respiratory rate was much slowed—in one case to 8 per min. and in the other to 6 per min.—with a correspondingly severe fall in tidal volume and in blood-pressure. In each case there was a brisk response to intravenous levallorphan (1·5 mg.), and neither patient gave further cause for concern.

From the above observations it would seem that both the qualitative and quantitative tolerance to dihydrohydroxycodeinone pectinate is high in dosage sufficient to give adequate and lasting pain relief during the postoperative period.

Summary

Dihydrohydroxycodeinone pectinate merits further evaluation as it appears to have definite advantages over many drugs at present used for postoperative analgesia. As the drug is broken down extremely slowly and there is little or no euphoric effect, addiction should not be a problem.

Conclusion

Dihydrohydroxycodeinone pectinate (' Proladone ') was tested in 600 patients who had undergone major operations.

It provided adequate relief of postoperative pain, following a wide range of major operative procedures, for periods up to three times that usually afforded by morphine, pethidine, and similar opiates.

The drug appeared to be well tolerated by patients of all ages and to have a wide safety margin. With dosage sufficient to provide adequate analgesia, side-effects were rare and slight.

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Medical Societies

ASSOCIATION OF CLINICAL PATHOLOGISTS AND ASSOCIATION OF CLINICAL BIOCHEMISTS

A JOINT meeting was held in London on Oct. 3.

Thyroid Antibodies

Dr. T. R. ROITT and Dr. Deborah DONIACH described the two completely independent immune systems in Hashimoto's thyroiditis. One of the antigens is thyroglobulin, present in the acinar colloid, antibodies to which can be demonstrated in 90% of cases of Hashimoto's thyroiditis, using the precipitation-in-gel or tanned-red-cell technique. The other antigen, an intracellular constituent located in the microsome fraction of thyroid epithelial cells, gives rise to complement-fixing antibodies in over 90% of Hashimoto patients. Certain cases of Hashimoto's disease have antibodies against a colloid constituent which is not thyroglobulin. These two types of antibody can be distinguished by the Coons fluorescent technique, in which the thyroglobulin antibodies are seen to stain the colloid in alcohol-fixed sections, while complement-fixing antibodies stain the cytoplasm of cells in frozen sections. Lymphadenoid lesions are thought to be due to autoimmunisation, but, despite the frequent occurrence of focal lesions in goitres, particularly thyrotoxicosis, progressive destruction of the gland is infrequent.

The antibodies described seem inadequate to account for the progressive lesions in Hashimoto's disease, although the sera have been found to include a constituent which is cytotoxic for thyroid cells in early tissue-cultures; the nature of this substance is unknown. In experimental autoallergic disease, delayed hypersensitivity is thought to cause the cell damage, but evidence for this effect in human thyroid disease is inconclusive. The question whether autoantibodies are the cause of the disease, or secondary results from a previous lesion, is not yet settled.

Dr. J. R. ANDERSON, Dr. R. B. GOUDIE, and Miss KATHLEEN GRAY described the complement-fixing antibodies which react with saline extracts of thyroid tissue. This reaction is positive in 90% of cases of Hashimoto's disease, over 50% of thyrotoxicosis and primary myxœdema, and 7% of hospital patients with no clinical evidence of thyroid disease. This apparently normal group consisted mostly of elderly women who proved to have chronic focal thyroiditis. This lesion is identical with that in Hashimoto's disease, and is also seen in some cases of myxœdema. Hashimoto's disease and primary myxœdema form a continuous series. The complement-fixation test, being positive in such various thyroid states, is of little help in diagnosis. By contrast, the precipitin test for circulating antithyroglobulin is positive only in clinically significant thyroiditis (Hashimoto's disease, myxœdema, or severe focal thyroiditis in thyrotoxicosis). Surgical treatment should be undertaken in these patients only when there is strong suspicion of carcinoma, or when medical treatment fails.

Dr. W. R. TROTTER, discussing the question of the antibody being responsible for the destructive lesions in the thyroid, said that there was reasonable correlation between the level of antibodies and the intensity of the destructive process. The antibody may be produced inside the thyroid gland in large amounts, that in the plasma appearing as an overflow. Clinically he has found the tests of practical value in detecting mild hyperthyroidism. A positive antibody test is a good indication of a destructive lesion.

Enzymes, Esterases, Cholinesterase

Dr. W. N. ALDRIDGE said that the cholinesterases are not specific for the hydrolysis of choline esters, but will hydrolyse non-choline esters also. Therefore it is important to determine the substrate to be used. Cholinesterases are less specific than ali-esterases, which can hardly hydrolyse choline esters. The substrate to use is an ester of choline with a positive charge. He described the two types of cholinesterase—the true and the pseudo. The true is present in red blood-cells and nervous tissue, and hydrolyses acetylcholine faster than the higher homologues. The pseudo is present in plasma, pancreas, and other tissues, and in man it hydrolyses butyryl choline faster than acetylcholine. It is possible to analyse a mixture of true and pseudo enzymes by using a mixed substrate of acetyl β-methyl choline and benzoyl choline, the latter being little hydrolysed by the true enzyme.

All the routine methods depend on the measurement of the acid formed by hydrolysis. For general use on tissues, &c., the manometric measurement of carbon dioxide formed from bicarbonate is the method of choice. The titrimetric method is good but tedious. Other suitable methods measure the change in pH. For screening in the field, a simple assay depending on the change in an indicator with time is used. A colorimetric method with β-carbonaphthoxycholine iodine as substrate has been described recently and appears to be worth further trial.

Prof. R. H. S. THOMPSON stressed the difference between the pseudo and true enzymes, the true being concerned with hydrolysis of physiologically released acetylcholine, while the function of the pseudo is unknown. If the pseudo enzyme is reduced to a low level, no effect on the acetylcholine content of the body is observed. B. McArdle showed how estimation of pseudocholinesterase can be used as a liver-function test, to differentiate between jaundice of hepatic or obstructive origin, the level being reduced in hepatic jaundice and cirrhosis but little changed in obstruction. That this fall follows diminished synthesis by the damaged liver is shown by the slower rate of regeneration after poisoning by di-isopropyl fluorophosphate. Low levels are found also in malnutrition, where the fall in cholinesterase is relatively greater than that of the serum-protein. Poisoning with organo-phosphorus compounds is accompanied by lowering of the serum-cholinesterase. Even minor and clinally undetected intoxication in cases of prolonged exposure can be shown up by lowered cholinesterase. In view of the wide range of normal figures, it is important to established a baseline in workers with these compounds before exposure. The action of succinylcholine as a relaxant drug is brief because it is rapidly hydrolysed by cholinesterase, but in patients with a low cholinesterase following liver disease, or in the rare individuals with genetic deficiency of the enzyme, lengthy apnœa may result from administration of the drug. Raised levels of cholinesterase are found in diabetics, but only in the obese, and a similar rise is found in non-diabetic obese persons. High levels are found also in the nephrotic syndrome. The cholinesterase is not abnormal in myasthenia gravis. Low levels of pseudocholinesterase in the skin have been found in cholinogenic urticaria—which agrees with the report that wealing is due to an abnormal over-reaction of the skin to the normal amount of acetylcholine released at the nerve-endings.

Mr. D. R. DAVIES said that the organo-phosphates are poisonous because they inactivate the cholinesterase by phosphorylating the active centre of the enzyme. Death is due to respiratory failure. Until three years ago, atropine was the sole antidote. Possible lines of treatment would be to find a compound phosphorylated as rapidly as or more rapidly than the cholinesterase, and thus to protect the enzyme by competition for the poison, or to activate the enzyme by dephosphorylating it. Such a compound must have high reactivity with organophosphoryl compounds, or with the phosphorylated enzyme. Possible types are *o*-dihydroxybenzenes—e.g. DOPA, metal

chelates, hydroxylamine, hydroxamic acids, and oximes. Derivatives of hydroxyiminomethyl-*N*-methylpyridinium have proved the most satisfactory. The compound 2-hydroxyiminomethyl-*N*-methyl pyridinium (2 PAM) has been used very successfully in conjunction with atropine for treating animals and man. In man it is relatively harmless in doses of 30 mg. per kg. In Japan, with 1000 cases of poisoning by 'Parathion' per year, PAM has been successful in most cases. Of 39 patients treated, only 1 died.

Assessment of Liver Disease

Mr. A. H. HUNT and Dr. H. LEHMANN contributed a paper on serum-albumin, pseudocholinesterase, and transaminases in the assessment of liver disease, before and after portacaval and lienorenal anastomosis. In 367 cases of cirrhosis the concentrations of serum-albumin, pseudocholinesterase, and, in some, transaminase were determined, in order to assess the suitability of cases for diversion of portal blood. The conclusions were: (1) that no patient should be submitted to shunt operation with a serum-albumin of less than 3·2 g. per 100 ml.; (2) that pseudocholinesterase fluctuates more than albumin, but that a level of 35 units is on the borderline. Of all liver-function tests, the serum-albumin gives the greatest help, and alterations in pseudocholinesterase give an estimate of the day-to-day response. Ascites is not a contraindication, provided preoperative treatment raises the values to a good level. Transaminase levels vary so much that they do not assist in assessment. They may indicate activity of disease, but not the degree of liver incapacity, which is what the surgeon wants to know.

Serum-isocitric-dehydrogenase

The colorimetric estimation of serum *iso*citric dehydrogenase was discussed by Miss JOYCE BELL and Dr. D. N. BARON, who described a colorimetric method in which the oxoglutarate formed from *iso*citrate and triphosphopyridine nucleotide by the action of the enzyme plus manganese is measured as the phenylhydrazone.

Enzyme Activities in Colon

Dr. R. A. DALE reported the measurement of enzyme activities in extracts of epithelial cells from normal mucosa and from carcinomas of the colon. The ratios of activity of lactate dehydrogenase, aldolase, and DNase in carcinomas to those in normal mucosa were respectively 2·0, 0·8, and 1·0.

Galactosæmia

Dr. J. H. WILKINSON reported the application of the method of E. P. Anderson et al. for determining galactose-l-phosphate uridyl transferase to red-cell hæmolysates from two cases of galactosæmia. In the first case, a healthy boy of 6 in whom galactosæmia had been diagnosed in infancy, and who had been reared on a galactose-free diet, there was no activity in the blood-hæmolysate. The normal range is 5·9–12·8 units per g. of hæmoglobin. The second patient, a girl aged 9 weeks, found to have galactosuria, had a normal transferase activity of 6·8 units. Dr. Wilkinson suggested that some other defect is responsible here for the galactosuria.

Urine-protein

Miss E. A. BUTLER and Dr. F. V. FLYNN reported a new urine-protein abnormality. In studying the proteinuria of renal tubular disorders by starch-gel electrophoresis, after concentration of the urine, 36 patients were found to have a small post-γ fraction. Of these, 14 had Fanconi's syndrome, and 9 had myelomatosis. This post-γ protein was found in the serum of 2 of the cases. Its presence in the urine is unlikely to have been due to denaturation, formation of a metal complex, or genitourinary-tract secretion. The protein failed to react to antisera to normal serum-proteins.

Secretory Response

The secretory response of gastropepsin, mucoproteose, and glandular mucoprotein to histamine as well as insulin stimulation was described by Dr. J. SCHRAGER. In the various patterns, the most noteworthy feature was the production of normal pepsin, with urine pepsinogen low or absent.

Reviews of Books

Treatment of Diabetes Mellitus

E. P. JOSLIN, A.M., M.D., SC.D., clinical professor of medicine emeritus, Harvard Medical School; H. F. ROOT, M.D., H.H.D., medical director, Joslin Clinic; PRISCILLA WHITE, M.D., SC.D., assistant professor in pædiatrics, Tufts University Medical School; ALEXANDER MARBLE, A.M., M.D., assistant clinical professor of medicine, Harvard Medical School. London: Henry Kimpton. 1959. Pp. 778. 122*s.* 6*d.*

Joslin's textbook has long been the most authoritative account of the clinical aspects of diabetes mellitus, and it is appropriate that the tenth edition should be published as the senior author achieves nonagenarian status. The 1959 edition is only 20 pages longer than the 1952 one, and yet it includes a new section on the oral hypoglycæmic drugs and excellent new contributions on the intermediary metabolism of diabetes by Dr. A. E. Renold and on the water and electrolyte disturbances in diabetic acidosis by Dr. Nancy Nichols. The Joslin Clinic is renowned for its tenet that the complications of diabetes can be long delayed or prevented by consistently good diabetic control. This theme constantly recurs in this book, supported by the results obtained in the authors' extensive experience. A welcome addition to future editions would be a few illustrations of typical diabetic manifestations, such as retinopathy and necrobiosis lipoidica diabeticorum, which Dr. Priscilla White finds in 1 out of every 50 young diabetics. The references could also be given in a more convenient form. The book ends with 30 pages of useful tables giving diets and normal body-weights for different ages and heights.

L'Hérédité Moleculaire

Conditions normales et pathologiques. JEAN DE GROUCHY. Rome: Edizioni dell'Istituto Gregorio Mendel. 1958. Pp. 333. 5000 lire.

THE respectability of human genetics is sufficiently new that there are notably few good books on this increasingly important subject. This book on molecular heredity by de Grouchy is of special interest, since it may be considered to supplement—but not replace—earlier works, such as those of Penrose, for it gives a more detailed picture of the recent biochemical advances in a variety of hereditary diseases.

There has been a series of remarkable advances in our understanding of the nature of the gene, but these advances have not yet impinged very forcibly on many human geneticists or clinicians. This little book bridges the gap between genetics and clinical medicine in an extremely effective way. The author, who is a physician, devotes more than half his space to discussing various inherited syndromes in man in the light of modern genetical and biochemical theory. The section on the abnormal hæmoglobins is particularly good. His emphasis on this subject has been amply justified by the exciting researches of Ingram, Vinograd, and others which had barely begun at the time this book was written. It is probably wrong to select a particular dish in a well-balanced meal, but the chapters on galactosæmia and Wilson's disease seem outstanding.

A prefatory series of chapters develop the concepts of modern genetical theory. D.N.A., pseudoallelism, and the mode of action of genes are among the important subjects discussed. But perhaps the most striking characteristic of the author's handling of these subjects is the originality of his approach and the clarity of his exposition. It is a pity that he did not include a chapter on methods in human genetics. The Hardy-Weinberg law is barely mentioned, and the subject of consanguinity could have received fuller treatment with advantage.

The book is superbly printed and the clear illustrations are of great value. A selected list of key references follows each chapter. The book is without an index, and we hope the next edition will have one. The French should prove a stumbling-block only to those who have forgotten completely their few years of schoolboy French, for the author has a taut and easy style, which is a pleasure to read. We recommend the book unreservedly to anyone interested in the heritable disorders of man.

The Viruses: Biochemical, Biological, and Biophysical Properties

Vol. 3. Animul Viruses. Editors: Sir MACFARLANE BURNET, Walter and Eliza Hall Institute of Medical Research, Melbourne; W. M. STANLEY, Virus Laboratory, University of California. New York and London: Academic Press. 1959. Pp. 428. 86*s*.

VOLUME 3 of this comprehensive systematic treatise is concerned with virus-host interactions at the cellular level using, where possible, at least three viruses (vaccinia, influenza A, and poliovirus) as models. The editors point out that the prevention and cure of virus diseases will depend upon greater knowledge of virus-host cell interactions. The book is devoted to comprehensive reviews of the experimental work by experts in the various branches. Virology is coming to occupy a key place in biological experimentation, and the great development in technique is enabling a direct attack on the problems of protein synthesis and genetic control. The feeling that new advances may render the book rapidly out of date is common to many contributors, but is most explicitly referred to by Andervont in his review of the tumour viruses. "This chapter may have been written at the poorest possible time. The problems of the tumour viruses are being advanced so rapidly through excellent investigations of the known viruses, the concentration of effort upon mouse leukæmia, the convergence of virus research and tissue-culture research that within a few years definitive answers may be had to the viral causation of many other cancers."

Virologists and biologists in related fields will be grateful for these excellent presentations organised out of the jungle of virological literature. They will learn what is now known and also what remains yet to be achieved. There is, however, less that is of direct interest, as yet, to the clinician or epidemiologist, although in the chapter on variation and virulence, Fenner and Cairns review the adaptations that have occurred amongst virus and host populations following the introduction of myxomatosis infection into wild rabbits in Australia, France, and Great Britain.

Odd Man Out

Homosexuality in Men and Women. EUSTACE CHESSER, L.R.C.P.E. London: Victor Gollancz. 1959. Pp. 192. 12*s*. 6*d*.

THE "cause", as distinct from the psychogenesis, of homosexual behaviour in human beings is, like that of most other events, unknown. The cause of the violence of the reaction to such behaviour in our own culture is known in part. And Dr. Chesser really aims less to explain the one than to moderate the other. He covers most of the ground: his strongest point is a sensibly compassionate insight into the feelings of people disturbed by their own impulses, his weakest a tendency to general statement in edifying terms which blurs the meaning of the psychological processes he considers, and an over-ready identification of his own ethical value judgments with "normality". Questions like the relative contributions of genotype and environment to sexual behaviour-pattern, and the significance in primate evolution of the Freudian castration-fear, for example, call for harder-headed biological treatment, though he is more critical than in previous books in approaching the idea of "innate" homosexuality, if still a little inclined to undervalue the Freudian explanation, and its possible comparative and developmental implications. He is not, however, writing a learned work—the reader, whether bothered by his own impulses or not, will at least acquire the idea that homosexual motives and behaviour are a part of the human inheritance, that gross overemphasis on them has some connection with childhood identifications, and may be susceptible to psychiatric treatment, and that the persecution of a socially unimportant form of conduct is itself a sexual deviation. This is all to the good, and if the book lacks intellectual edge it is at least on the side of good sense.

Wolff's Diseases of the Eye (5th ed. London: Cassell. 1959. Pp. 266. 42*s*.).—The fifth edition of this book for general practitioners, junior residents, and medical students, has been carefully revised by Mr. Redmond Smith, some of it rewritten, and the work brought up to date. It is admirably illustrated. The English of the previous editions seldom made fluent reading so the new author had a hard task in marrying his style with the old. It might have been well to add to the differential diagnosis of acute glaucoma the fact that exploratory laparotomy for intestinal obstruction and indeed craniotomy are sometimes done on mistaking the significance of the symptoms and signs. Advice about the treatment of basal-cell carcinoma and squamous-cell epithelioma of the eyelids is indefinite and should be firmly in favour of surgery. It is of course unimportant for medical students to know more than the outlines of the commoner operations of eye-surgery but some points in this chapter could with advantage be altered in the next edition. In the modern operation for cataract there is no need to ask the patient to "look down", nor at the end of operation on being told to shut his eye could he possibly do so after an effective facial-nerve block. Such instruments as the conjunctival forceps, Prince's muscle clamp, Müller's lacrimal speculum, the squint hook, and Moorfields' bandage (mask) have been much improved upon during the past 20 years. Many eye surgeons consider cocaine undesirable for corneal abrasions, and because of the damage of pressure keratitis would not favour "tight" bandaging—a better word would be "firm". Such criticisms are minor. The book is beautifully produced.

New Inventions

A FLEXIBLE ŒSOPHAGOSCOPE

IN a busy endoscopy clinic it is essential to be able to carry out many œsophagoscopies on both inpatients and outpatients under local anæsthesia only. Hitherto, however, flexible instruments available in this country have been unsatisfactory in that a narrow lumen allowed only poor vision and prohibited the passage of a useful size of bougie. Distal lighting was quickly obscured by œsophageal contents or blood, and the passage of a suction tube completely blocked vision.

The instrument illustrated here was made to my specification by the Genito-Urinary Manufacturing Company in 1956 with the aim of remedying these defects. I have now completed approximately 100 examinations with it, all under amethocaine anæsthesia (either lozenges or solution), and I believe it has the required advantages. It allows examination for distances up to 50 cm. from the incisor teeth. With the inner rigid tube in position a size-18 English G.E. bougie can be passed easily, and without it a size-24 English bougie. Excellent intensity and focus are obtained from a proximal movable bronchoscope-type lighting system, and a built-in suction tube allows continuous aspiration controllable by a stopcock.

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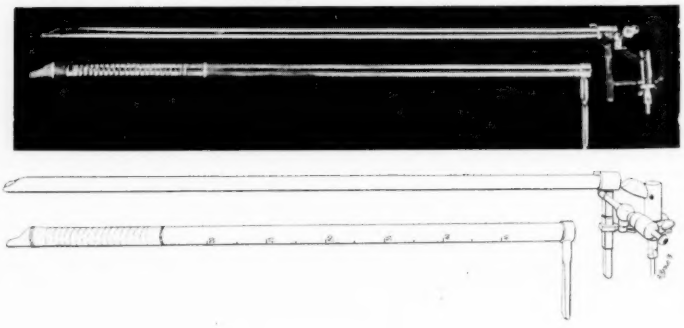

THE LANCET
LONDON 10 OCTOBER 1959

Premature Induction and Rh-Antibody Titre

PREMATURE induction of labour, by removing the fœtus from the source of antibody, has long seemed a possible method for minimising the severity of hæmolytic disease of the newborn. But premature induction itself carries risks to mother and fœtus,[1 6] while prematurity, especially associated with hæmolytic disease of the newborn, can be dangerous.[7 9] A controlled trial comparing premature induction and spontaneous delivery in this disease [10] suggested that, although some stillbirths were prevented by induction, this was offset by an increase in neonatal deaths, so that the final results favoured spontaneous delivery. Moreover the severity of disease, judged by cord hæmoglobin values, was the same in liveborn infants whether or not labour had been induced.[11] It seems therefore that if premature induction has anything to offer, it is essentially in the prevention of stillbirth.[12] With the proper use of exchange transfusion, repeated if necessary, the neonatal death-rate from hæmolytic disease of the newborn can be reduced to less than 5%,[13 14] but such a low rate is not being achieved generally.[15] Until it is, indiscriminate premature induction is likely to lead to loss rather than saving of life.

Intrauterine death due to hæmolytic disease of the newborn may occur as early as the 18th week of gestation [16]; so induction, though preventing some stillbirths,[10 17] can never provide a complete solution. A reliable method of forecasting stillbirth is required, and this should if possible also foretell when intrauterine death is likely. WALKER and his colleagues [18 19] studied the family history in relation to stillbirth and concluded that, although the overall risk is 15%, this varies with the previous history being only 7% in the pregnancy in which antibodies first develop but 70–80% when one or more preceding pregnancies have ended in stillbirth. They put the risk of stillbirth at 20% in a pregnancy following the birth of a moderately affected infant but at over 50% if the preceding infant has been very severely affected or stillborn; and they advocate induction in such cases provided the father is homozygous but admit that only 50% of such pregnancies reach 35 weeks' gestation—the time selected for induction.[20] They calculate that induction, to be 50% successful where there has been more than one previous stillbirth, would have to be undertaken at 32 weeks. On the other hand induction at 37 weeks could prevent 60% of stillbirths where the previous offspring had "moderate" disease and 70% of stillbirths in the pregnancy in which antibodies initially develop. The previous history, then, is of limited value, for where the indication for induction is clearest prospect of benefit is smallest. FREISLEBEN [21] states that "given the titre, the condition is dependent on the history, and conversely given the history, the condition is dependent on the titre"; the maternal antibody titre might certainly be expected to be of value in prognosis, for MOLLISON [22] has shown that the rate of red-cell breakdown is related to the dose of antibody attached to the cells. Antibody titre is correlated to some extent with the severity of hæmolytic disease of the newborn [9]; but exceptions are common,[23 26] and the value of the titre in individual cases has been questioned.[8 12 27]

Elsewhere in this issue Dr. TOVEY and Dr. VALAES describe a "combined approach" at Bristol. Realising that the greatest reward from premature induction is to be obtained in cases where antibodies are developing for the first time, they have concentrated on such cases. By induction at 37 weeks' gestation they have avoided the hazards of severe prematurity, while induction itself has presented no problems. Other workers,[19 28] inducing labour at 32 or 35 weeks' gestation, have reported difficulties concerning both mother and infant and have attributed a substantial proportion of their neonatal deaths to induction itself. Because the chance of spontaneous livebirth increases the closer a pregnancy approaches term satisfactorily,[12 20 29] in the reported Bristol series the risk of stillbirth at 37 weeks would be only 5%. When playing for such small stakes selection must be precise, for even in the best hands induction carries some risk. TOVEY and VALAES compare their 88% survival-rate with one of 84% reported for a similar but "spontaneous" series from Newcastle.[30] These results are not significantly different, and had the Bristol workers been less skilled in achieving premature delivery or in their care of the newborn infant the figures might have told a different story. Both series appear to show a better survival-rate than the 73·5% and 77% survival reported by Australian workers in two series treated by selective induction,[31 32] but in a disease with so varied a pattern comparisons of different series can be misleading.

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The two techniques for measuring antibodies most commonly used in antenatal work are the albumin method [21 33–35] and the indirect Coombs technique.[36 37]

KELSALL and his coworkers refer to erratic results obtained by the albumin method but claim that, carefully performed, the indirect Coombs test will give reliable and reproducible results [36 38]; and this method is preferred by TOVEY and VALAES. Various precautions have been recommended in order to minimise errors,[12 24 40–42] but even with the greatest care FREISLEBEN [21] found that 6% of samples tested in duplicate showed errors of more than two dilutions.

The Australian workers now state that the indirect Coombs technique can be misleading and that, for instance, a titre of 1 in 1024 may be associated with all degrees of severity from stillbirth at 35 weeks' gestation to mild disease that requires no treatment or even an Rh-negative fœtus. Regretting that no-one had devised a simple test with a high probability of predicting severity they have now described a partial absorption technique [32 38] in which the serum is absorbed with an arbitrary quantity of Rh-positive cells after which titration is carried out by the indirect Coombs method. This technique, they claim, enables prognosis to be assessed more accurately than with the indirect Coombs method. They found that sera with a titre of 1 in 1024 by the indirect Coombs technique might have a partial-absorption titre varying from nil to 1 in 1024. In 90% of cases the partial-absorption corresponded exactly with, or was within one dilution of, the level of "free antibody" present in the infant's serum; this level, like ALLOTT and HOLMAN [23] and DIAMOND et al.,[43] but unlike MOLLISON and CUTBUSH,[44] they feel reflects the severity of disease in the infant.

TOVEY and VALAES base their recommendation on "the maximum titre obtained, at or before, the time of gestation at which premature delivery might have to be considered" and recommend induction if the indirect Coombs titre is 1 in 40 or higher at 36 weeks in a first-affected pregnancy but 1 in 10 or 1 in 20 in subsequent pregnancies. VOS,[38] regarded a titre of 1 in 64 or less as having no pathological significance but recommended induction if the titre approached 1 in 512—the level above which almost all fœtal loss occurred.[39]

Because prognosis based on isolated titres has led to conflicting opinions, workers have investigated the influence of the time during which antibodies are present. CHOWN and BOWMAN [26] and FREISLEBEN [21] consider that the prognosis is worse the earlier antibodies develop, and correspondingly PALMER and REQUIAM [25] consider that late immunisation is rarely serious. VAUGHAN [12] goes further in suggesting that antibodies are of relatively little importance in the pregnancy during which they develop, but KELSALL and his colleagues [17 37] report that in more than half their cases dangerous levels developed after the 34th week of gestation. This is surprising; for in England at least, routine antibody tests are often carried out only between the 32nd and 36th week of pregnancy and there is no reason to believe that this had led to many cases being overlooked. KELSALL et al.[32 39] suggested that prognosis could be improved if the antibody level was evaluated from the 26th week of pregnancy onwards by calculating a titre index for this period. Exceptions still occurred: of 43 Rh-negative infants, 17 were associated with high titre indices (40–60), while 5 were subjected to premature induction because the titre index was over 60.

If antibody titre is to be of practical value it should enable a forecast to be made of the probability of stillbirth or the presence of an Rh-negative fœtus in families where the father is heterozygous. Because discrepancies between titre and outcome are common, attempts have been made to decide the prognosis by studying variations in titre during pregnancy. Many workers regard a rising titre as an indication of severe disease and perhaps as an indication for induction,[27 33 36 45] but others consider that severe disease may be associated with a fall in titre [23 43] or with little change.[46] A rising or stationary titre has been recorded in association with an Rh-negative fœtus,[25 35] but MOLLISON [47] regarded a twentyfold increase as indicating that the fœtus was Rh-positive. ZUELGER,[48] however, recorded a titre rise from 1 in 2 to 1 in 1024 during the latter part of a pregnancy in which the fœtus was nevertheless Rh-negative. The Australian workers [38] admit that there is no certain way of forecasting the presence of an Rh-negative fœtus but consider that the partial-absorption titre is superior to the indirect Coombs titre in this respect, and especially that a low partial-absorption titre in the presence of a high indirect Coombs titre indicates this.

It is extremely difficult to reconcile all these conflicting views on the importance of antibody titre, but KELSALL and VOS [37] suggest that episodes of immunisation occur which vary in magnitude with the number of fœtal cells entering the maternal circulation. They cite cases to support this hypothesis, and certainly the abrupt and often pronounced changes in titre could be explained in this way. Whether the recognition of such episodes will prove of value in managing this disease remains to be proved, but it seems that some of their cases that resulted in spontaneous stillbirth met their earlier published criteria for induction.

At present no single feature before birth enables the severity of hæmolytic disease of the newborn to be forecast accurately, but evaluation of the previous history in conjunction with the present antibody titre will help in many instances. The approach of TOVEY and VALAES is essentially practical: realising the shortcoming of antibody titre and premature induction, they have concentrated on cases where induction has most to offer. But induction is no complete solution: we cannot resign ourselves to continued failure to prevent the stillbirth that occurs before 34 weeks' gestation.

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Intermittent Peritoneal Lavage

IT has long been known that the peritoneum can act as a form of dialysing membrane between the blood and fluids in the peritoneal cavity.[1] The area of the peritoneum has been estimated at about 20,000 sq. cm.,[2 3] which is somewhat larger than the glomerular filtration area in the kidneys [4–7]; and it would seem reasonable in renal failure to employ this large dialysing area to rid the body of noxious products normally excreted in the urine. In principle all that is necessary is to place in the peritoneal cavity a solution which permits diffusion of those substances requiring removal (and nothing else), to allow time for the dialysis, and then to remove the fluid, replacing it as required by a fresh supply. But in practice these steps have not proved easy, and peritoneal lavage, peritoneal dialysis, or peritoneal kidney (to give it some of its names) has run into many difficulties.

First used in man by GANTER in 1923 [8] and occasionally afterwards, this method did not "catch on" until the painstaking systematic work of FINE, FRANK, and SELIGMAN in 1946 [9 10] established its usefulness. In this country the first case was reported in the same year by REID, PENFOLD, and JONES,[11] and REID described five further cases in 1948.[12] FINE et al. used a continuous technique whereby fluid was run into one side of the abdomen by a tube and out of the other by another tube with an uninterrupted flow of fluid through the peritoneal cavity, sometimes for long periods. REID et al., on the other hand, ran the fluid into the peritoneal cavity through a tube, left it there for a given period, usually two hours (the time in which the blood and dialysate were known to reach equilibrium), and then removed the fluid through the same tube, repeating the procedure as necessary. The benefits and dangers of the two methods, continuous and intermittent, have been debated ever since. A third method, "short-term continuous dialysis", was introduced in France [13 14] and used in America by LEGRAIN and MERRILL.[15 16] It consists essentially in short periods (up to fifteen hours) of continuous dialysis, repeated as necessary after a rest period. DEROT and BERNIER [17] state that they have performed 366 such dialyses in 204 patients over the past ten years. Though each of these methods has had its advocates, on the whole the scales have come down in favour of the intermittent method. This was due largely to the work of GROLLMAN et al.[18 19] in Dallas. GROLLMAN pointed out that the dangers of dialysis—namely, peritonitis and œdema, and particularly pulmonary œdema—were slighter with the intermittent method, and that it was much less complex than the continuous method. The intermittent method can be applied in any hospital boasting a surgeon who can put a tube into the peritoneum in a watertight fashion and a laboratory able to estimate urea and electrolytes in blood and dialysate; but the patient requires from both surgeon and pathologist most careful supervision and attention to detail.

First tried in 1914 by ABEL, ROWNTREE, and TURNER,[20] extracorporeal dialysis was reintroduced in the war years by KOLFF,[7] who ran the blood through a 'Cellophane' tube in a bath of dialysing fluid. This "artificial kidney" has tended to displace peritoneal lavage in the treatment of acute renal failure, as it is highly efficient, although complex, and of course the patient is not liable to peritonitis. For many years the conservative treatment of anuria had been quite irrational, but the BULL regime [21] with balanced water and electrolyte intake and output and a diet to decrease protein catabolism, giving the kidneys longer to recover, provided a sound and easy conservative means of treating acute renal failure. Accordingly this regime has become standard practice with, at some big centres, the occasional use of an "artificial kidney" and elsewhere the very occasional use of peritoneal lavage.

That this relative neglect of peritoneal lavage may be unsound is suggested by a report by DOOLAN et al.[22] from the U.S. Naval Hospital at Oakland, California. By various means, including intermittent peritoneal lavage, they treated ten cases of acute and chronic renal disease, with mainly satisfactory results. Of the three possible major complications of this method—water and electrolyte imbalance, blockage of the peritoneal tube, and peritonitis—the first presented no trouble, as a carefully balanced dialysing fluid was used together with frequent blood analyses and a constant check on the body-weight. Blockage of the peritoneal tube by kinking, blood-clots, or omentum has taxed the inventiveness and patience of many workers; but DOOLAN et al. claim to have much reduced the risk of this by using a polyvinyl tube, made to their own design, and inserted well into the pelvis through a small neat watertight infraumbilical surgical incision. Peritonitis developed in only one case; but it had to be constantly watched for and, if noticed, immediately treated.

If, as DOOLAN et al. suggest, these complications can be controlled, "intermittent peritoneal lavage is an effective means of treating the clinical and chemical manifestations of uremia". It is especially useful in patients with œdema, particularly in the lungs, in potassium intoxication, and in cases where a slower chemical change than that brought about by the "artificial kidney" is required. Poisons, too—for instance, salicylates and other drugs—can be removed by peritoneal lavage. In 1957 TAYLOR [23] suggested that the usual conservative methods might be inappropriate in the post-traumatic

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23. Taylor, W. H. *Lancet*, 1957, ii, 703.

form of renal failure; and here too peritoneal lavage might prove useful. Anuria that does not respond well to conservative treatment, and chronic renal failure with acute exacerbations, are often much ameliorated by peritoneal dialysis. This is obviously no " silver bullet " for renal failure; but in suitable cases it is a good leaden bullet, which should perhaps be fired more commonly than at present.

Dr. Joslin's Ninetieth Birthday

A RECENT issue of the *New England Journal of Medicine* [1] is dedicated to Dr. ELLIOT P. JOSLIN on his 90th birthday. It contains nine papers on diabetes from various countries, as well as tributes from, among others, Prof. CHARLES BEST, Prof. BERNARDO HOUSSAY, and Dr. R. D. LAWRENCE.

It is hard for most of us to picture the changes that Dr. Joslin has seen during his life, or even since he treated his first diabetic in the Massachusetts General Hospital in 1893. The discovery of pancreatic diabetes, the control of diabetes by food restriction, the discovery of insulin, the demonstration of the role of the liver in the regulation of the blood-sugar, the action of hormones on the metabolism of carbohydrate, protein, and fat, and the oral hypoglycæmic drugs—these are some of the headlines of progress that have fascinated him and improved the treatment that he could offer his patients. At 90 his mind is, as ever, alert and interested, especially in problems of diabetes all over the world. His body does not lag behind, and he arrives punctually at the Joslin Clinic at 8 A.M. each morning.

JOSLIN'S influence in diabetes is too great to be explained only by time, and it is interesting to consider why he has held so much authority for so long. No-one who meets him can fail to be impressed by his dedication to the work of improving the outlook for diabetics and by his conviction that this can be achieved only by rigorous regard for the factors which may divert the blood-sugar level from normal. His conviction and his enthusiasm are the means by which he has persuaded so many of his patients to discipline their lives.

But he is not a man of one approach: he has offered as tangible incentives two medals—a bronze one, which has already been awarded to more than 3000 patients who have lived longer with diabetes than they would have been expected to live without it, and a gold medal, awarded to more than 80 patients who show no signs of complications after having had the disease for twenty-five years. One of his latest innovations on his home ground is a teaching clinic where ambulatory diabetics learn more in less time and at less cost than under the old bed-patient system. Less locally, but equally characteristically, he has encouraged summer camps for diabetic children. Last year he visited Düsseldorf to attend the congress of the International Diabetes Federation, in which he has always taken a warm interest, and he contributed in no small measure to the success of the meeting.

His influence has overstepped the circle of his own patients, and, through successive editions of his textbook, *The Treatment of Diabetes Mellitus*, has reached people all over the world. The first edition was published in 1916, and the tenth edition (reviewed on p. 547) crystallises the experiences of over 50,000 diabetics seen in the Joslin Clinic. Part of Dr. JOSLIN'S message is expressed simply enough in the lines inscribed on the walls of his clinic:

> Who learns and learns
> Yet does not what he knows,
> Is one who plows and plows
> Yet never sows.

1. *New Engl. J. Med.* Aug. 27, 1959.

Annotations

RENAL CALCULI IN POLIOMYELITIS

RENAL calculi are apt to develop in patients who are immobilised for a long time from any cause; and at the symposium of the European Association against Poliomyelitis (which is briefly described by a correspondent on p. 560 of this issue) one of the topics was urolithiasis in this disease. F. Larsen and Philip described a careful study in which they followed up 1607 patients for five and a half to six years after the onset of poliomyelitis in the Danish epidemic of 1952–53, and found renal calculi in 40. (Since their diagnostic criteria were strict the true incidence may have been higher.)

They showed that urolithiasis is especially likely in adults, males, patients with severe paralysis, patients immobilised for a long time, patients who have been treated by respirator, and patients who have had urinary infection. This list of precipitating factors may be more repetitive than it seems at first. Adults are more severely affected by poliomyelitis than children, in that they tend to have more severe and extensive paralysis, and also to recover function in affected muscles less completely. Males moreover are more seriously affected than females: deaths in males amount to about one and a half times those in females.[1] Patients immobilised for a long time and those who have been treated with a respirator are clearly, as a group, nearly identical with patients with severe paralysis. Possibly, therefore, the incidence of renal calculi reflects the severity of the disease, and many of the factors found by Larsen and Philip to be associated with urolithiasis exert their influence because they tend to be associated with severe paralysis. Another factor mentioned by Larsen and Philip was urinary infection. This is commoner in the severely paralysed than in the less severely paralysed. But here the degree of paralysis is not the only determinant; these workers found that among a group of patients severely enough paralysed to require respirator treatment there was no instance of calculi where the urine was uninfected, whereas calculi were found in 28% of those with urinary infection. The great importance of urinary infection as a causal factor is therefore clear. The relation of artificial respiration to renal calculi is also of interest. These workers found that, among patients with triplegia or tetraplegia, renal calculus developed in 25% where a respirator was required but in none where a respirator was not required. Here again the greater severity of the disease, and consequently the more complete immobilisation, in those requiring a respirator may be of dominant importance; but it is nevertheless possible that long-continued use of a respirator may itself promote calculus formation,

1. Martin, W. J. *Mon. Bull. Minist. Hlth Lab. Serv.* 1959, **18**, 54.

especially as most patients receiving artificial respiration are over-ventilated and the resulting alkalinity of the urine favours calculus formation.

In the prevention of calculi high fluid intake and frequent changes of posture are important. Mobilisation helps also in treatment; for small calculi are the nuclei of large calculi, and by mobilisation severely paralysed patients may be enabled to void small calculi.[2] (One patient, paralysed from the neck downwards, recommends driving over French pavé for this purpose.) If large calculi develop, surgical treatment is both desirable and possible even in patients with respiratory involvement.

There is one further preventive measure which is practicable but is too rarely practised—namely, the avoidance of urinary infection in the catheterised patient. This is especially important because infection, once present, is extremely difficult to eradicate.[3] If catheterisation is regarded as a surgical operation and is performed with surgical technique, using sterile gloves and gown, urinary infection can be avoided; for catheterisation is not usually required in poliomyelitis for more than two or three weeks. Some paraplegic units have already adopted this routine, which should perhaps be followed in catheterisation for any reason.

CROSS-INFECTION

IN the prevention of staphylococcal cross-infection in hospitals precept is easy but practice difficult. Coles [4] remarks of maternity wards that "In the presence of staphylococcal sepsis early identification of cases, sterilising the blankets, oiling the floors, laying the dust, training the staff, cleaning the cords, dealing with carriers . . . do not instantly abolish sepsis"—though since his work was done in 1956–57 new techniques have been introduced, such as the application of antiseptics to the umbilicus and the use of hexachlorophane baths and dusting-powder, which help to prevent the skin colonisation which forms such an important reservoir of infection in a nursery.[5] Williams et al.[6] faced the problem in its most intractable form—a busy general hospital in which staphylococci of phage-type 80 and other tetracycline-resistant strains were already established among patients and staff. They report that "attempts at wholesale elimination of the infection were undertaken and failed" for these reasons: (1) it was impossible to isolate symptomless carriers of these strains as well as patients and staff with clinical infection; (2) in some people nasal or skin carriage persisted despite treatment; and (3) foci of infection with tetracycline-resistant staphylococci are increasing outside hospitals, so it is becoming difficult to avoid the introduction of virulent strains with new admissions.

Some workers have cut short an outbreak by detecting and removing a few carriers of the epidemic strain,[7 8] but the task of picking out carriers who are likely to be dangerous from the staff and patients of a large general hospital is enormous. At least two swabs must be taken, at an interval of a week or more, in order to find out whether carriage is transient or permanent. Staphylococci should be phage-typed, for an antibiotic-resistance pattern may be the same for many different strains. Moreover, an individual may be a heavy distributor of staphylococci from a site other than the nostrils, such as the perineum.[9] Once a heavy carrier of a dangerous strain has been detected, what chance is there of cure? Intensive and conscientious use of nasal ointments containing antibiotics such as neomycin and bacitracin, of chlorhexidine hand-cream, and of hexachlorophane baths and soap will be effective in most cases; but those which do not respond must each be considered as a separate problem. Williams et al. suggest that for both carriers and people with lesions isolation is essential, but the need for this surely depends on the spreading potentiality of the carrier. Some have been shown to disseminate their organisms more widely than others,[10] while the danger of spread from infected patients varies with the kind of lesion. For example, a closed abscess is much less dangerous than a discharging wound, lung infection, or skin disease; one such case can do more damage than a wardfull of nasal carriers and must be effectively isolated. As Rountree et al.[7] stated in 1956, there is no chance of an epidemic subsiding as long as a heavy carrier of the epidemic strain is present.

It takes courage to refuse to use a drug which may do good, but there is no doubt that penicillin and the tetracyclines are becoming less and less likely to be of value. Clinical workers should remember that bacteriologists put tetracycline in their blood-agar plates in order to select strains which are likely to be virulent. An antibiotic should not be used without bacteriological proof that the infecting organism is sensitive to it—and ideally the patient should be isolated during the course of treatment. Work by Barber et al.[11] suggests that administration of antibiotics in pairs helps to prevent the development of resistance.

When phage-typing is at the disposal of every hospital, the bacteriological contribution will be almost complete. Dangerous carriers can now be identified once the epidemic strain or strains have been recognised, but in most hospitals the resources to deal with these—notably of nurses and beds—are sorely deficient.

SEROLOGICAL TESTS BEFORE ADOPTION

UNDER the new Adoption Regulations [12] infants who are to be adopted must be submitted at the age of not less than 6 weeks to standard serological tests for syphilis. It has been suggested that where the mother's Wassermann reaction is known to have been negative during the pregnancy such tests are superfluous,[13] but a negative reaction during the pregnancy does not in fact preclude syphilis in the offspring: the mother may transmit infection while in the incubation period of syphilis or in the seronegative primary stage; and, as in a case described by Dr. Lees,[14] she may acquire infection during pregnancy after the Wassermann reaction of her blood has been tested.

Infected infants are sometimes serologically negative at first, but serological tests become positive usually by the age of 4 weeks and nearly always by the age of 6 weeks. In small infants it is difficult to obtain blood from the arm, but not from the heel. One technique is as follows:

Immerse the child's foot in hot water for a few minutes. Dry and apply a light tourniquet round the lower leg. Sterilise the skin of the fleshy part of the heel with spirit. After a few minutes stab the heel with a Hagedorn needle or make a small snick through the skin of the heel with a sterile safety-razor blade. The blood flows freely and

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10. Hare, R., Thomas, C. G. A. *ibid.* 1956, ii, 840.
11. Barber, M., Csillag, A., Medway, A. J. *ibid.* 1958, ii, 1377.
12. Adoption Act, 1958: Adoption Agencies Regulations, 1959, no. 639.
13. Black, J. *Lancet*, Aug. 29, 1959, p. 239.
14. Lees, R. *ibid.* Sept. 12, 1959, p. 348.

can be collected in a test-tube; 2 ml. of whole blood is sufficient. The clean cut made by the blade is practically painless; bleeding soon stops when the tourniquet is removed, and healing is prompt.

Congenital syphilis is on the wane, but an appreciable number of cases is notified each year. We believe that the new regulations are reasonable, because this infection responds to therapy in infancy, and it is in the infant's interest that the infection should be discovered and treated.

ARTHRITIS AND ULCERATIVE COLITIS

ARTHRITIS is said to be the commonest complication of ulcerative colitis outside the intestinal tract [1]; estimates of its incidence have ranged from 4% to 22%. There has been some doubt as to whether this is a specific form of arthritis or whether it is rheumatoid arthritis, and, if the latter, whether the association is merely one of chance.

Bywaters and Ansell [2] conclude from a detailed analysis of 37 cases that there exists, in association with ulcerative colitis, a form of arthritis separate from rheumatoid disease. It consists characteristically of mild recurrent migratory synovitis, sometimes remitting with improvement in the gut symptoms. The joints most commonly involved are the knees and ankles, but the proximal and distal interphalangeal joints of the toes (seldom affected in rheumatoid arthritis) or the sacroiliac joints may be involved. The radiographic findings are similar to those in rheumatoid arthritis, with osteoporosis and articular bone erosion, and the sacroiliac changes are indistinguishable from those of ankylosing spondylitis. The histological appearance of the synovial membrane is also similar to that in rheumatoid joints. The Rose-Waaler sheep-erythrocyte agglutination test, however, is negative; but 2 of Bywaters and Ansell's patients with ulcerative colitis had classical rheumatoid arthritis and a positive Rose-Waaler test—a finding ascribed by these workers to the chance coexistence of the two disorders. McEwen et al.[3] also report a negative Rose-Waaler test in 22 patients with ulcerative colitis and arthritis, 15 of whom had peripheral-joint involvement and 7 characteristic ankylosing spondylitis.

Using another approach, Fernandez-Herlihy [4] has examined 555 case-records of ulcerative colitis diagnosed at the Lahey Clinic over a thirty-year period. Despite the limitations of such a retrospective study, some interesting observations emerge. After the exclusion of osteoarthritis, traumatic arthritis, and rheumatic fever, articular manifestations were present in 95 patients (17% of the total).

These joint disorders could be divided into five categories. The commonest (28 cases) was "rheumatoid spondylitis", identified by typical radiographic evidence of sacroiliac involvement. The second category (23 cases) was peripheral-joint arthralgia without clinical or radiographic evidence of articular swelling or damage. Third in frequency came "definite rheumatoid arthritis" [5] (18 cases). Unfortunately serological tests for rheumatoid arthritis were not available, and uncertainty about the classification of "definite rheumatoid arthritis" has since led the American Rheumatism Association to revise their criteria and introduce the more rigorously defined group of "classical rheumatoid arthritis".[6] The fourth category consisted of erythema nodosum (16 cases), associated in every instance with arthralgia or acute arthritis. (Erythema nodosum occurred in 8 of the 37 cases of Bywaters and Ansell). The fifth category (10 cases) was large-joint polyarthritis closely corresponding in time to activity of the colitis, and termed "acute toxic arthritis".

Such a subdivision may be useful in determining the management of individual patients. In cases with arthralgia, erythema nodosum, or "acute toxic arthritis", the joint symptoms were found to correlate with the severity of the colitis, and nearly always remitted after colectomy. Spondylitis and rheumatoid-type arthritis, on the other hand, usually continued to progress after colectomy.

In the past ten years our ideas about rheumatoid arthritis have been modified by the development of the Rose-Waaler test and its variations, with their high degree of specificity for classical rheumatoid arthritis (almost 100% positive in cases with nodules). There are several syndromes, including the arthritis of ulcerative colitis, Reiter's disease, psoriatic arthritis, and ankylosing spondylitis, which are sometimes called "rheumatoid arthritis variants". Negative agglutination tests in these conditions, however, together with clinical differences shown by such careful studies as those mentioned here, suggest that these disorders are distinct from rheumatoid arthritis.

BONE CHANGES AFTER BURNS

SOME bone atrophy takes place in all severely burned patients, and is probably due, as Artz and Reiss [1] stated, to increased adrenocortical activity and to prolonged immobilisation. Colson et al.[2] emphasised that reflex vasomotor disturbances may also play a part; reactions of this type are presumably responsible for localised, rather than general, bone atrophy.

Other changes which follow burns have been classified by Evans and Smith [3] as periosteal new-bone formation, pericapsular calcification, osteophyte formation, and heterotopic para-articular ossification. The formation of new bone by the periosteum or joint capsule is nearly always associated with loss of skin over the overlying or an adjacent area. Deposits may remain small and localised or may spread until joints are severely involved. True para-articular osseous bridging may occur in the unburnt extremity, and Johnson [4] suggested that this was due to the trauma of routine care. Ossification of this type is more commonly recognised in paraplegics, and clearly a wide variety of traumatic incidents may result in para-articular formation of new bone.

Surgical excision of newly formed bone must be delayed until it is mature; and in children, unless it produces complete ankylosis, excision is rarely, if ever, required. The prognosis, as far as joint function is concerned, is often good. By contrast, intra-articular joint changes, which are usually the result of infection, often at a distance, carry a poor prognosis, and are rarely improved by surgical intervention.

In the burned patient, bone and joint changes other than osteoporosis are rare, and Evans and Smith were able to find only 20 examples in a review of 950 patients. The pathogenesis of these changes, as in most other examples of ectopic new-bone formation, remains obscure.

Mr. R. RUTSON JAMES, consulting ophthalmic surgeon to St. George's Hospital, London, died at his home at Woodbridge, Suffolk, on Sept. 28.

1. Bargen, J. A., Jackman, R. J., Kerr, J. G. *Ann. intern. Med.* 1938, **12**, 339.
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Special Articles

A GENERAL THEORY OF NATIONAL EXPENDITURE ON MEDICAL CARE

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SINCE 1948 nearly all expenditure on medical care in Great Britain has been by the National Health Service. Since then the annual expenditure by the service has been accurately known and widely publicised, and has risen each year. The actual annual gross cost of the service and its continued rise has caused surprise and concern to many, and there is a widespread feeling that it ought to cost less.

This paper does not attempt to answer the question of how much a nation ought to spend on medical care, for answers to this question are value judgments on which agreement cannot be expected. It attempts to answer the questions of how much does a nation spend on medical care and how can its future expenditure be predicted.

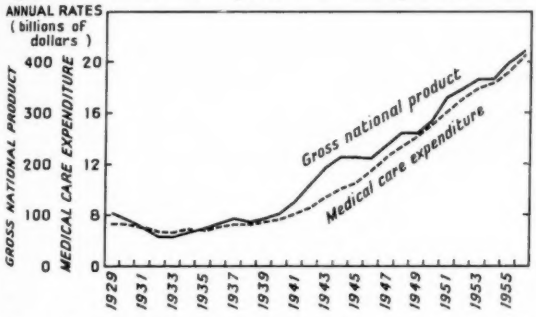

Fig. 1—Gross national product and national expenditure on medical care, U.S.A., 1929–56.

A PRELIMINARY HYPOTHESIS

National expenditure on medical care in any given year must come from national income. The most casual observations suggest that nations with a high national income such as Britain, the U.S.A., and Switzerland have a higher per-capita expenditure on medical care than nations with a low national income such as India, Egypt, and Mexico. These observations lead one to formulate the preliminary hypothesis that national expenditure on medical care is related to national income.

This hypothesis can be verified or refuted by more detailed observations.

National expenditure on medical care is the gross aggregate expenditure, by all private individuals and organisations and by all public authorities, on medical care in any given year. Medical care includes the services of hospitals, doctors, dentists, opticians, and public-health authorities, and the supply of drugs, medical appliances, and medical-care insurance. These are the services and goods supplied by the National Health Service in Great Britain.

A widely used measure of national income is known technically as the gross national product. This is the totality of goods and services produced by a nation during one year for both consumption and investment, expressed in monetary units such as pounds or dollars.

MEDICAL CARE EXPENDITURE IN THE U.S.A.

Data with which the above hypothesis can be tested are available for the U.S.A. for each year since 1929. The table gives a detailed analysis of national expenditure on medical care in the U.S.A. from 1929 to 1956. Fig. 1 shows the national expenditure on medical care and the gross national product, and fig. 2 shows the former expressed as a percentage of the latter for each year from 1929 to 1956 in the U.S.A.

These data indicate that national expenditure on medical care in the U.S.A. is very closely related to national income. There has been little variation in the proportion of the gross national product devoted to medical care during these twenty-eight years in spite of considerable changes in the general and medical economy.

The 1930s saw the greatest economic depression in American history and the 1940s the greatest foreign war. The gross national product rose by nearly eight times between 1933 and 1956 in actual prices and it rose over three times in constant prices.

During these same years there have been considerable changes in the science and practice of medicine. These changes have been accompanied by important changes in medical economics. Over 70% of all United States citizens now have some form of private prepaid medical insurance, compared with less than 5% in 1929. At the same time the public authorities have increased their share of the national expenditure on medical care from 13% in 1929 to 26% in 1956.

These data from the U.S.A. thus strongly suggest the following provisional theory:

The proportion of the gross national product of a nation devoted to medical care tends to remain constant.

The data show that there has been some variation in the proportion in the U.S.A. during these years. The factors that tend to stabilise the proportion will now be considered, followed by an examination of those factors with which variations are associated. The provisional theory will then be re-examined.

FACTORS STABILISING NATIONAL EXPENDITURE ON MEDICAL CARE

Two conflicting groups of forces act on national expenditure on medical care. Medical, social, economic, and

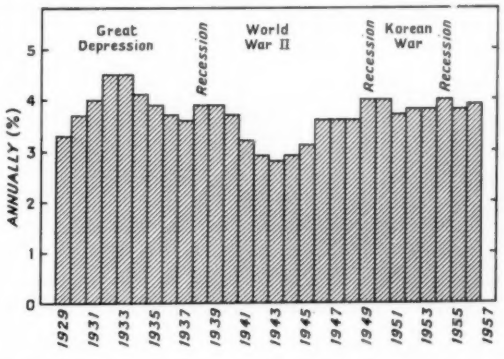

Fig. 2—National expenditure on medical care expressed as a percentage of gross national product, U.S.A., 1929–56.

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political forces tending to push up expenditure are balanced by the limitation of private and public funds which prevent expenditure rising beyond a certain level. In addition there are factors of inertia which tend to keep actual expenditure constant.

Forces of Expansion

Medical.—It is often thought that advances in medicine resulting in the prevention of individual diseases or the cure of individual patients will result in a healthier population and therefore a diminution in the need for medical care. This is confused thinking.

It is quite true that the virtual disappearance of many infectious and deficiency diseases from the populations of wealthy nations has made serious illness or death in children and young adults unusual in these nations except in war. The result, however, has not been a decrease in the prevalence of disease, but an alteration in the pattern of disease in the population. The great majority of persons in these nations after relatively healthy and economically productive early years now live on to middle or old age when they become susceptible to other diseases, particularly neoplastic and degenerative. Characteristically these diseases of the older age-groups are chronic, and preventive and therapeutic measures are largely ineffective and very expensive. It is highly improbable that this situation will ever change fundamentally, because death is inevitable and not usually preceded by perfect health.

Not only has improved medical care altered the pattern of disease, but the pattern changes as new diseases appear or rare diseases become common for reasons that are imperfectly understood. Coronary-artery disease and carcinoma of the bronchus, which were both clinical curiosities before 1900, are now major causes of death and morbidity in the middle-aged, the increased incidence being largely independent of increased expectation of life. There is no justification in assuming that changes in the disease pattern will not continue in the future.

As medical science becomes more exact and effective it also becomes more complex. The application of radiology, biochemistry, and electrodiagnosis gives more exact diagnoses, and the development of neurosurgery, cardiac surgery, and radiotherapy gives more effective treatment than formerly; but these methods are complex and expensive and will become increasingly so. At the same time patient and doctor alike usually expect a more accurate diagnosis more promptly than formerly, resulting in recourse to extensive diagnostic investigations and to specialist advice for symptoms that previously would have been ignored or received some inexpensive placebo.

Social.—The expectations of a nation of its standard of medical care will affect its expenditure on medical care. These expectations rise as the standard of living rises,

NATIONAL EXPENDITURE ON MEDICAL CARE, U.S.A., 1929–56
(Million dollars)

—	Personal-consumption expenditure							Public-authority expenditure				Total	—	
								State	Federal					
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
	Drug preparations and sundries	Ophthalmic products and orthopædic appliances	Doctors	Dentists	Other professional services	Privately controlled hospitals and sanatoria	Medical care and hospital insurance	State and local authorities	Veterans' service hospital and medical care	Promotion of public health	Medical care for military services	National expenditure on medical care	Gross national product	Ratio of medical care expenditure to gross national product (%)
1929	604	131	959	482	250	403	108	390	30	15	4	3376	104,400	3·3
1930	568	133	924	463	233	404	110	440	36	16	5	3332	91,100	3·7
1931	517	117	819	408	201	395	92	448	41	17	4	3059	76,300	4·0
1932	449	93	661	312	154	386	72	456	54	19	4	2658	58,500	4·5
1933	427	92	617	276	138	363	70	437	58	17	4	2499	56,000	4·5
1934	468	124	678	295	145	369	85	418	59	15	3	2659	65,000	4·1
1935	474	131	731	302	191	406	93	443	62	15	3	2851	72,500	3·9
1936	509	140	820	331	165	422	106	467	69	22	3	3054	82,700	3·7
1937	558	165	854	350	168	454	123	509	72	27	3	3283	90,800	3·6
1938	578	157	833	356	163	467	134	551	71	29	4	3343	85,200	3·9
1939	612	172	866	386	167	492	153	580	72	32	4	3536	91,100	3·9
1940	635	186	913	419	173	527	165	609	78	36	7	3748	100,600	3·7
1941	725	227	957	459	179	555	196	600	79	37	49	4063	125,800	3·2
1942	848	258	1048	505	196	649	231	591	84	43	143	4596	159,100	2·9
1943	1014	307	1092	539	206	752	279	624	84	59	530	5486	192,500	2·8
1944	1072	333	1321	573	245	846	315	656	101	152	477	6091	211,400	2·9
1945	1138	349	1370	620	266	925	374	737	118	186	418	6501	213,500	3·1
1946	1271	396	1720	772	338	1163	444	818	216	173	264	7575	210,600	3·6
1947	1313	400	2020	784	390	1397	513	1023	461	146	105	8552	234,300	3·6
1948	1358	427	2203	833	423	1591	550	1229	592	139	78	9423	259,400	3·6
1949	1350	448	2312	857	448	1730	557	1488	737	171	119	10,217	258,100	4·0
1950	1406	479	2435	869	478	1975	636	1748	764	242	193	11,225	284,600	4·0
1951	1516	532	2528	888	498	2167	651	1966	745	304	261	12,056	329,000	3·7
1952	1569	561	2676	906	532	2398	740	2185	784	328	449	13,128	347,000	3·8
1953	1615	577	2815	943	562	2602	887	2290	757	316	398	13,762	365,400	3·8
1954	1631	566	2913	975	583	2852	1078	2409	782	290	314	14,393	363,100	4·0
1955	1747	572	3070	1017	610	3130	1126	2524	727	275	277	15,075	397,500	3·8
1956	1885	612	3269	1070	646	3451	1173	2772	788	351	296	16,313	419,200	3·9

SOURCES

Column

1–7 1929–53 "National Income" (1954) U.S. Department of Commerce, table 30.
1954–56 "Survey of Current Business" (July, 1956 and 1957) U.S. Department of Commerce, table 30.

8 "Facts and Figures of Government Finance" (1958–59) Tax Foundation Inc. N.Y., p. 138. Only alternate years given up to 1952. Estimates for years not given are calculated as being half-way between the preceding and succeeding years.

9 1940–56 "Facts and Figures of Government Finance" (1958–59), p. 85. 1929–39 U.S. Government Budgets Actual Expenditure.

10–11 U.S. Government Budgets Actual Expenditure.

13 "Survey of Current Business" (July, 1958) U.S. Department of Commerce.

DETAILS

Column

5 Includes private nurses, chiropodists, osteopaths, &c.

6 Comprises current expenditure (including depreciation) of non-profit hospitals and payment by patients to proprietary hospitals.

7 Premiums less claims (profit-making and non-profit-making insurance).

8 Expenditure on health and hospitals by States and local authorities (grants-in-aid by Federal Government not included).

10 Direct expenditure by Federal Government plus grants-in-aid.

11 Medical and hospital department of Army, plus medical care Navy, plus medical support Air Force.
Medical-care expenditure by industry and philanthropy are not included.

just as the expectations of the individual rise as his standard of living rises. The citizens of a wealthy nation who regularly eat good and plentiful food, live in comfortable homes, and have much leisure, expect to have hospitals that are new, bright, clean, and heated, that have good food, small rooms, and extensive laboratory and radiological facilities, and where much personal attention from doctors and nurses is available. In addition they expect ambulances, casualty departments, operating-theatres, blood-transfusion units, doctors, nurses, and empty hospital beds to be ready day and night in case one of them is struck down by a motorcar. These services are expensive, and the expectations can only be translated into practice by increasing expenditure.

Economic.—As industrialisation increases and national income rises, the real earnings of the industrial workers, technicians, and managers rise and their hours of work fall. These changes are gradually reflected in the earnings and hours of work of those employed in the medical-care and other services; for, if they are not, personnel will tend to leave these services. The effects of rising wages on costs in industry can often be offset by increased efficiency through mechanisation, resulting in a smaller labour force for unit production. Mechanisation is less applicable to medical care, which largely consists of personal services; and consequently, in an expanding economy, the cost of the same medical care will rise even without general price inflation. This is particularly marked with hospital care, where industry competes directly for the services of most of the non-professional personnel.

Political.—In a modern democracy the pressures on politicians to spend public funds on medical services are strong. Sanitation, control of infectious diseases, and food inspection are obvious public responsibilities and have been so considered for many years. In recent years, however, expenditure of public funds on personal health services has greatly increased in many countries, public authorities gradually increasing both the range of services provided and the sections of the population covered. This expansion has tended to follow the broadening of the electoral base. Public provision of personal health services has been peculiarly attractive to politicians because not only are they helping to avert hardship and tragedy in many individual cases, but in so doing they attract the votes and support of the population to whom the medical care is being supplied at little direct cost and thus enhance their own position of power.

Limiting Factors

The forces pushing up national medical-care expenditure are held in check by the limitation of private and public funds and by other demands on these funds. The needs for food, clothing, warmth, and shelter are greater than the need for medical care, and even after these basic needs are satisfied there are innumerable other desirable ways of using financial resources apart from medical-care expenditure or insurance.

The private funds of even many wealthy people do not suffice to pay for the best medical care available in all circumstances. Private insurance also has inadequate funds for such services for all the insured, because the insured are unable or unwilling to pay the very high premiums required. The State has inadequate funds for such services for all the population because the taxpayers are unwilling or unable to accept the very high taxes required. The result collectively is therefore a compromise. A nation cannot have the medical care it needs, it can only have the medical care it can afford or is willing to pay for. In practice this remains a fairly constant proportion of national income.

Factors of Inertia

Examination of total expenditure on medical care shows that 70–80% is on wages, salaries, and professional services. Much of this represents the services of many highly skilled persons who have had a long and specialised training. Surgeons, neurologists, dentists, nursing sisters, physiotherapists, and radiographers cannot suddenly be multiplied because of increased economic demand. Nor do they readily forsake their vocation for more lucrative employment elsewhere. Nor can their services be dispensed with abruptly by the public when funds are short because of the recurrent and permanent nature of the demands of ill health. The result is that the number of persons employed in medical care fluctuates less than in certain other occupations such as the armed Services or shipbuilding, and actual expenditure for their services is more nearly constant.

FACTORS CAUSING VARIATIONS IN THE PROPORTION

Fig. 2 shows that the proportion of the gross national product in the U.S.A. devoted to medical care has not remained quite constant.

In the early 1930s it rose from 3·3% in 1929 to 4·5% in 1933 falling again in the late 1930s. This reflects the changes caused by the most profound and prolonged economic depression in American history. Between 1929 and 1933 the gross national product nearly halved while expenditure on medical care dropped by less than a third. This difference can be explained by the factors of inertia noted above. The net effect was a rise in the proportion.

In the early 1940s the proportion dropped from 3·9% in 1939 to 2·8% in 1943; in the late 1940s it rose again. This reflects the changes caused by the most intense and prolonged foreign war in American history. The factors of inertia again explain this changing ratio. During the war the gross national product rose rapidly with the great expansion of employment in the armed Services and the war industries, but the expenditure on medical care rose less rapidly because the Government diverted men and materials away from medical care into national defence. The net effect was a fall in the proportion.

The minor economic depressions of 1938, 1949, and 1954, and the war in Korea, all affected the ratio, but to a smaller extent.

THE THEORY RESTATED

The considerations above allow the theory to be restated as follows:

The proportion of the gross national product of a nation devoted to medical care tends to remain constant. It rises during national economic depressions and it falls during wars.

The data available for the U.S.A. for 1929–56 are consistent with this theory. The general applicability of the theory can be confirmed or refuted by observations in other nations. However, even before this is done, a moment's reflection will suggest that the theory is inadequate.

In the U.S.A. in the past ten years between 3·6% and 4·0% of gross national product has been spent on medical care. But only 12% of the labour force is employed in agricultural production. India, on the other hand, has 70% of its labour force so employed. India clearly

cannot spend such a high proportion of its gross national product on medical care as can the U.S.A. It thus seems probable that when national per-capita income rises nations can and do spare an increasing proportion of their total income for medical care. The data available for the U.S.A. for 1929–56 neither confirm nor refute this assumption; for any increase in proportion is likely to be detectable only over a period of many decades and after real per-capita national income has increased several times. It may well be that the historical data required to show this trend in an individual nation do not at present exist, because accurate and detailed national income statistics are a comparative innovation.

The general theory in its final form is thus:

The proportion of the gross national product of a nation devoted to medical care tends to remain constant. It rises during national economic depressions and it falls during wars. A persistent rise in real per capita gross national product will tend to result in a very gradual increase in the proportion.

APPLICABILITY OF THE THEORY TO OTHER NATIONS

The data presented are derived only from the U.S.A. Though the theory postulated is consistent with these data, the criticism might be made that it is not applicable to other nations and that data from other nations are required before its general applicability can be claimed.

It is highly probable that a similar relationship to that observed in the U.S.A. between national expenditure on medical care and the gross national product will be found to apply in other nations with similar economic systems. The theory does not imply anything very startling. It implies that the medical-care "industry" is relatively stable economically. It implies that the needs of a nation for medical care are never satisfied but that additional funds are made available only in proportion to increased national income. It implies that the medical-care field can and does expand as the general economy expands and not independently of it. It implies that very wealthy nations spend a greater proportion of their national income on medical care than do very poor nations. None of these implications appears particularly unrealistic.

CENTRALLY CONTROLLED MEDICAL-CARE FINANCING

This theory is a statement of observed relationships. It states what does occur, it does not state what ought to occur. I am not suggesting that it is some unchangeable, iron, economic law.

In a nation where virtually all medical care is supplied by a health service under central financial control, with funds derived from taxation, the health-service planners are in a position to ignore this relationship if they so desire. They can decide that the proportion of the gross national product spent on the health service shall be raised or lowered, or they can take action which would tend to have such effects, though they are unaware of any such relationship. But if they did ignore it, certain predictable difficulties would be encountered.

If the proportion of gross national product spent on the health service was to rise rapidly over a few years, certain effects could be foreseen. To raise the proportion would imply that personnel were transferring from other occupations to the service; or that the average earnings of those already in it were rising more rapidly than in the rest of the population; or that there was a relatively heavy investment of capital in the service; or some combination of these. In a period of full employment this would tend to force up earnings in other industries and thus stabilise the proportion again. In addition the rapid rise in taxes that would be required to finance the health service would be unpopular among the population on whose votes the position of power of the health-service planners depended.

If the proportion were to drop rapidly over a few years other difficulties would arise. A fall in the proportion would imply that personnel were transferring from the health service to other occupations; or that their average earnings were falling relative to the rest of the population; or that the service was being starved of capital; or some combination of these. If earnings dropped persistently there would be difficulty in staffing the health service because of greater attractions elsewhere, and there would be increasing dissatisfaction among the specialised professional and technical personnel who were unable to move. If carried too far for too long, the result would be a deteriorating health service using dilapidated buildings employing disgruntled personnel in a dissatisfied community. To avert this undesirable situation pressure for more funds would mount, thus tending to stabilise the proportion again.

It thus seems highly probable that even in those nations where expenditure on medical care is planned under central control the general theory would still be applicable in the long run. It is likely that if central control of medical-care expenditure passed abruptly to health-service planners who were unaware of the difficulties that would be encountered by rapidly altering the relationship, then considerable variations in the proportion might occur. After a few years, however, the stabilising forces would have their effect, and a more usual relationship between health-service expenditure and the national income would prevail.

CONCLUSIONS

The rise in national expenditure on medical care that has taken place in many countries since the second world war can firstly be attributed to the change from a war-time to a peace-time economy, and secondly to rising national income. Expenditure will continue to rise as long as national income rises.

In a democracy central authorities find it difficult to alter the gross national expenditure on medical care in the long run apart from controlling national income. They can, however, alter the sources of funds. These sources may be distributed in a great variety of ways between central authorities, local authorities, private insurance, payments by patients, and philanthropy.

The national expenditure on medical care may remain a fairly constant proportion of gross national product, but the distribution of expenditure within the various categories of medical care and within the various organisations may vary widely. For example, fever hospitals and children's hospitals may close but geriatric hospitals expand, or expenditure on general practitioners may fall relative to expenditure on drugs.

Though the provision of medical care must take place within the setting of national income, actual national expenditure on it is no indication of the need for medical care within the nation and little indication of the quality or effectiveness of the care provided.

SUMMARY

National expenditure on medical care has been compared with gross national product in the U.S.A. between 1929 and 1956.

From the data obtained a general theory of national expenditure on medical care has been postulated. This theory states that the proportion of the gross national product which a nation devotes to medical care tends to remain constant. It rises during national economic depressions and it falls during wars. A persistent rise in real per-capita gross national product will tend to increase the proportion very gradually.

This theory appears to be applicable not only to the U.S.A. but also to other nations with a similar economic system.

Difficulties that may occur in a democracy if the central authorities rapidly alter the relationship are considered.

Dialogues of Today

A MATTER OF LIFE AND DEATH

SOCRATES: I hear, Eryximachus, that someone has again been advocating a law to make it legal for a doctor to end the life of a patient who is suffering from a painful and incurable disease. What do you think of that proposal?

ERYXIMACHUS: It seems to me quite unnecessary, Socrates. It is very rarely that anyone suffers from pain which cannot be controlled by adequate doses of drugs. I have never known a doctor refuse to give enough of such drugs, and there are undoubtedly some who in such circumstances on their own responsibility give what amounts to a fatal dose to put an end to the patient's sufferings.

ENTHUSIASTICUS: That is exactly the case for legislation, Socrates. If a doctor gives a fatal dose, he is now legally guilty of murder. He should not be exposed to such a risk, nor should he alone undertake such a responsibility. Besides, is it fair to the patient to leave his fate in his doctor's hands? He may wish his sufferings ended, but the doctor may refuse on principle to carry out his request. In such circumstances the patient should have the right to have his wish granted, by another doctor, if not by his own.

THEOLOGUS: May I put in a word, Socrates; for I am bound to question what seems to be the premises of both Eryximachus and Enthusiasticus? I cannot agree that it is ever right to take a person's life in order to relieve his suffering.

SOCRATES: Why do you think that, Theologus?

THEOLOGUS: For the simple reason that it is wrong to take life.

ENTHUSIASTICUS: But, surely, Theologus, I have heard you maintain that capital punishment and, in certain circumstances, war are right.

THEOLOGUS: I agree that if a war is just it is right that a soldier should kill his enemy; for, though taking life is an evil, injustice may be a greater one.

ENTHUSIASTICUS: And if war entails the deaths of thousands of women and children, and perhaps the malformation of thousands yet unborn, is it still right?

THEOLOGUS: If the nature of war is such that justice can be established only by such means, then, terrible though its consequences may be, we should not shrink from it. But, to return to the original question, religion has laid it down that it is not wrong for a doctor in an incurable case to take the measures necessary for the relief of suffering, even though incidentally they shorten life.

SOCRATES: I am always anxious to learn all I can about religion, Theologus; so I must be sure I understand you aright. If I were a doctor with a patient dying of cancer in great pain, would it be right for me to give him drugs in sufficient doses to relieve his pain even though that shortened his life?

THEOLOGUS: Certainly.

SOCRATES: And would it make any difference whether I shortened his life by a greater or lesser amount, or would you say that it would be right to shorten it by a certain number of days, but wrong to shorten it by more?

THEOLOGUS: I do not see that the number of days makes any difference to the principle.

SOCRATES: Then suppose that I decide that in order to relieve his suffering I must give him a large enough dose to end his life today, would that, in the view of religion, be right or wrong?

THEOLOGUS: It would be wrong if your intention was to take your patient's life rather than to relieve his suffering.

SOCRATES: Now let me ask you some questions, Enthusiasticus. If the doctor who hastens his patient's end is to be safeguarded, there must, I suppose, be some legal process?

ENTHUSIASTICUS: Something of this kind would be required; but it need be no more than a consultation between the patient's doctor and an approved consultant, and the signing by the patient of a form wnich both doctors would witness.

SOCRATES: Have you thought of the patient's relatives? (For it would hardly be possible, or perhaps desirable, to keep this procedure secret.) Would the consent of a husband, wife, or child be necessary? And what would be the feelings of a wife asked to agree, against her will, to her husband's death, or if she knew that it was being brought about without her consent? And why should pain be the only reason for taking life? If you admit suffering as a justification, are there not many diseases of body and mind which cause distress as great as pain, and last much longer than most painful diseases? Why should not the same escape be permitted for them?

ENTHUSIASTICUS: Those are questions which had not occurred to me, Socrates.

SOCRATES: Well, Apollodorus, since we are told this is a legal question, give us your views as a lawyer.

APOLLODORUS: A lawyer is also a human being, Socrates, though some people seem to doubt it; and, apart from legislation, progress in legal theory depends, more perhaps than is realised, upon lawyers who are both human and humane. Legally, Enthusiasticus is right, though, apart from difficulties of proof, I do not see any jury finding a doctor guilty of murder because he hastened the end of a dying patient. And when once Theologus has conceded the principle that it is permissible to shorten life to relieve suffering, I can see no logical basis for the distinction he makes about the doctor's motive. The truth is that the laws relating to murder were not made with any such circumstances in mind. The term "malice aforethought" denotes only the intention to kill; but if the law is to be soundly based on ethics it must surely take account of motive, as in fact the present law of murder does. In which case it can rightly distinguish between killing in anger or for gain, and hastening death to relieve suffering. Common sense would say that in the one case the murderer kills and in the other the cancer. But if the law is out of date, should it not be brought up to date, as Enthusiasticus suggests? But tell us, Socrates, what you think?

SOCRATES: It seems to me that it is the quality of life which matters, rather than its duration; and I doubt if the purposes of the gods are served either by disease or by prolonging the mere fact of living. I have known the human spirit transmute suffering into greatness; but to die heroically in any circumstances is for the few, and must always be freely chosen. It would appear, then, that either doctors must be prepared to break a law which was made for a different purpose, or their action in hastening a patient's end must be given the form of law. We must all respect the laws, and not lightly disregard them; but are there not human situations which cannot be reduced to statutory terms? All the doctor's art and humanity are needed when he has to care for a dying patient and his friends. Can the law intervene here without doing harm? Are there not human reasons why a death certificate should not be given until after the event? I hope with you, Eryximachus, that we shall hear no more of legislation to enable men to die in peace, but that doctors will be ready to go on carrying their responsibilities in this as in so many other matters of life and death.

Conferences

CARDIOVASCULAR DISORDERS

FROM A CORRESPONDENT

THE fourth Meeting of the International Cardiovascular Society was held in Munich from Sept. 18 to 20.

Changing Concepts in Vascular Surgery

Dr. M. E. DEBAKEY (Houston, Texas), in the René Leriche lecture, spoke of the variety of ways in which the hæmodynamics of obstructed or diseased vessels can be restored: by endarterectomy; by excision and grafting; or by a bypass in which a channel is reconstituted without excision. The methods which he illustrated included multiple anastomoses, sometimes over a considerable length of blood-vessel. He emphasised that arteriosclerotic lesions were sometimes localised, and even though multiple could often be treated adequately.

Subsequent speakers included Prof. R. FONTAINE (Strasbourg) who, despite the current popularity of arterial homografts and prostheses, found that the use of veins in replacing arteries had proved valuable.

The remarks of other speakers suggested that crimped, knitted 'Dacron' and 'Teflon' tubes are in widespread use.

Prof. C. G. ROB (London) described the results of reconstruction operations after follow-ups of more than eighteen months. His preference was for a prosthesis in replacing or bypassing the aorta and larger vessels and for arterial homografts for vessels smaller than the femoral artery. He stressed that with artery grafts the best results were obtained by deep freezing and sterilisation with antibiotics.

High Atmospheric Pressure

Prof. I. BOEREMA (Amsterdam) demonstrated experimental work on animals under increased atmospheric pressure. By reducing the hæmoglobin as low as 5% it was possible to keep the animal alive in a pressure of three atmospheres. The plasma became saturated with oxygen, and this physical solution appeared to be adequate for the animal's basic needs.

Open Heart Surgery

Dr. W. G. BIGELOW (Toronto) said that open heart operations under hypothermia were undertaken at 29–31° C (the level accepted as the most suitable by subsequent speakers). 130 cases of atrial septal defect had been operated on under hypothermia, with 6 deaths. Extracorporeal circulation was reserved for more complicated atrial septal defects and for other conditions in which cooling was unsuitable. 10 cases of mitral insufficiency had been treated by annuloplasty with promising early results; there were 3 deaths. Prof. H. SWAN (Denver) also advocated surface cooling in simple cases and cited his experience in 280 cases, of which 149 were simple atrial septal defects (8 deaths) and 54 were pulmonary stenoses (no death). He also reserved perfusion for ventricular defects, auriculoventricular canals, and Fallot's tetrad; he was finding increasing benefit from a combination of perfusion and moderate hypothermia.

Mr. T. HOLMES SELLORS (London), discussing the surgery of atrial septal defects, cited 201 cases of secundum defect with 7 deaths; the mortality in 150 good-risk cases was less than 1%. Hypothermia was used exclusively in all secundum cases and perfusion was reserved for ostium primum defects. Prof. E. DERRA (Düsseldorf) said that atrial septal defect had been operated on in 273 cases with 20 deaths and 210 good results. His figure for anomalous venous drainage in secundum defects (20%) was four times greater than that given by Mr. Sellors.

Prof. C. CRAFOORD (Stockholm) emphasised how in the early stages of open-heart work the risks taken were often considerable and the results consequently much inferior to those obtained when technical problems had been solved and more suitable types of case were encountered. The difference between the early and bad-risk cases and the later and better-risk ones was striking, and illustrated clearly the progress that had been achieved.

Dr. C. DUBOST (Paris) discussed extracorporeal circulation in a series of over 150 cases. He pointed to the danger of operating on ventricular septal defects with severe pulmonary hypertension, cyanotic Fallot's tetrad, and auriculoventricular canals, where the mortality lay between 20 and 30%.

The views and results mentioned by different speakers were remarkably alike. Whereas the results of more simple operations under perfusion were steadily improving, these could not approach the good results obtained in the treatment of atrial septal defects and pure pulmonary stenosis under hypothermia. The problems of the auriculoventricular canal, hypertensive ventricular septal defects, and cyanotic Fallot's tetrad were still some way from solution.

Extracorporeal Circulation

Dr. DEBAKEY read a paper for Dr. D. A. COOLEY (Houston) on experiences with 600 cases treated with extracorporeal circulation. These included cases of acquired valvular disease and of aneurysm of the left ventricle, in addition to the types of cases already discussed. They also included 4 cases of myxoma of the left atrium in which the operation was successful. Altogether 12 cases of successful removal of myxoma were reported at the meeting.

Dr. DENIS MELROSE, Mr. W. P. CLELAND, and Mr. H. H. BENTALL (London) illustrated important aspects of extracorporeal circulation, including the necessity for keeping the venous pressure constant and for economy in the use of blood, the association of persistent ductus arteriosus with ventricular septal defects, and the problem of aortic incompetence during bypass. Prof. R. ZENKER (Munich) reported 70 cases of extracorporeal circulation, 11 with the help of hypothermia.

POLIOMYELITIS

FROM A CORRESPONDENT

THE sixth European Symposium on Poliomyelitis, with the participation of the German Society of Struggle against Poliomyelitis, was held in Munich on Sept. 6–9. As Prof. H. LASSEN said in his introduction, it was in Bavaria, at Stuttgart, that Heine in 1840 first described poliomyelitis, calling it *Spinale Kinderlähmung*.

Vaccination and Epidemiology

The first morning session was devoted to vaccination and epidemiology; a change from two years ago, when statistics of notifications was still the rule. Nearly all delegates spoke of the safety of the Salk or kindred vaccines. In the German Federal Republic, however, among 165,000 persons vaccinated 1 developed paralysis five days later and 3 had high pyrexia and transitory paralyses. None of the other 12 countries had serious trouble and even this exception did not seriously challenge the benefits, for in Germany 3 among 121,000 vaccinated and 153 among 539,000 non-vaccinated controls got poliomyelitis, the rates per 100,000 being 2·51 and 28·31. In some countries where vaccination is voluntary and free, the percentages "immunised" were very high; in Denmark 99% of those aged 9 months to 14 years had been immunised, 93% aged 15 to 19, and 85% aged 20 to 39. The incidence in Denmark in 1951–55, which included major epidemics in 1952 and 1953, was 15 per 100,000, and in 1956–59, the years of vaccination, 0·65. Dr. H. VON MAGNUS (Denmark) said that in a group of children, admitted to hospital for non-febrile illnesses, 5–8% excreted poliovirus.

In the United Kingdom satisfactory conversion-rates had been recorded, as judged by the production of antibodies, but the rates varied with different vaccines. Type-1 virus was the chief invader. 32% of children up to 15 and 73% of those aged 15–26 were unvaccinated. In Norway the occurrence of new cases among children vaccinated two or three times was 80% lower than in children vaccinated once or not at all.

The general opinion was that vaccination was harmless but caution was urged against too readily accepting the post-hoc-ergo-propter-hoc argument in favour of its efficacy.

Diseases Resembling Poliomyelitis

Professor PROCHAZKA (Czechoslovakia) spoke of tick-borne encephalitis, contracted by man from the bites of ticks or from infected goat's milk. In an epidemic affecting 300 admitted to hospital and involving an equal number of abortive cases, the virus was the same as " louping ill " and Russian tick-borne encephalitis. Clinically there was usually a febrile illness, an interval, then a second febrile illness with serious headache, occasionally followed by paralysis two to three weeks later. Fatigue was a constant aftermath in the long convalescence, but the later psychological disorders and loss of mental ability were in striking contrast to poliomyelitis; work might aggravate the disease. Possibly gamma-globulin helped in treatment. Death in the acute stage was rare.

Dr. V. DROUET (Paris) reported that from April, 1958, to April, 1959, in 106 children suspected of poliomyelitis, polio virus was isolated from 77, Echo virus from 14, Coxsackie viruses from 7, and adenoviruses from 5. Coxsackie B3 and B5 and Echo 6 and 12 are often associated with peripheral paralytic syndromes.

Dr. D. A. J. TYRRELL (England) spoke of volunteers given Echo virus or control material. Echo-20 virus isolated from American children admitted with fever, coryza, and abnormal stools, was used and the volunteers developed sore throat and fever. The disease was transmittable to others. Echo-11 virus, which had been " passaged " in human-embryo lung culture came originally from Swedish children with epidemic non-diphtheritic croup and minor respiratory illness. In the volunteers this caused abnormal discomfort or distension with diarrhœa in some. Controls were normal although the conditions were artificial, enteroviruses seemed able to cause respiratory symptoms.

Live Vaccine

Dr. ALBERT SABIN (U.S.A.), the chief guest speaker, discussed field trials with an oral live attenuated poliovirus vaccine, which differed from all other vaccines in that it produced a latent immunity and infection in those who swallowed it and spread to exposed persons. It multiplied in those partially or non-immune but not in immunes. Field trials had proved its safety. It was estimated that over the years for every 100–300 children who converted from susceptibility to immunity, 1 case of paralysis would occur. In other words, if a type-I strain multiplied and infected 1,000,000 susceptible people, 5000 cases of paralysis would occur. The absence of paralysis among the millions inoculated was valid evidence of safety. Spread to others was chiefly by fæcal contamination and by way of small children. To test its efficacy, between October, 1958, and June, 1959, 4,500,000 people (chiefly children) in Russia, Czechoslovakia, Singapore, and Mexico, where Salk vaccine had not been used, were given oral live vaccine. After 10 passages through children, no increased neurotropism was found. The organisms multiplied in children and adults with natural antibody or with Salk-produced antibody.

Whether to give type I, II, and III together or in any special order was important. Occasionally partial and complete suppression of one type occurred if another type is given. When type I was fed first, type III readily multiplied if given three to four weeks later, and type II readily terminated multiplication of type III after a similar interval. 96–100% then developed immunity to all types. Echo virus, Coxsackie, and adenoviruses could suppress multiplication of poliovirus in the gut, an important factor in unhygienic communities. The results of big field trials were still awaited.

Dr. J. D. VERLINDE (Holland) reported laboratory controlled trials in approximately 200 children and adults fed 100,000 to 1,000,000 tissue-culture infective doses of type I, type III, and type II polio viruses at intervals of three weeks. Alimentary infection lasted longer in children than in adults without pre-existing homotypic antibody. Infection might last seven weeks in those without antibody, and usually one to two weeks or less in those with antibody. The immunising effect in children without pre-existing homotypic antibody was 100% for types I and III, and 90% for types II. He emphasised that oral vaccine produced not only antibody but a relative resistance of the alimentary tract against all three types in almost 100% of individuals. He found a slight increase of neurovirulence in isolates in the second or third week after ingestion, but this seemed to be transitory and does not increase with subsequent passage in other individuals.

Dr. M. P. CHUMAKOV (U.S.S.R.) and his colleagues submitted a preliminary report on mass oral immunisation with live vaccine. As Salk vaccine does not protect from paralysis in 20–30%, since it is intramuscular or subcutaneous and requires repetition, live vaccine seemed to be more promising. The Russians had verified that mass vaccination of 6,250,000 persons was not accompanied by accidents, that children without pre-vaccination antibody developed it to the three types of poliovirus one month after oral vaccination with a trivalent mixture.

Dr. J. H. HALE, Dr. M. DORAISINGHAM, Dr. L. H. LEE, Dr. K. KANAGARATNAM, Dr. K. W. LEONG, and Dr. E. S. MONTEIRO (Singapore) described an experiment with live vaccine to control an epidemic of poliomyelitis in Singapore. In September, 1958, when it was evident that type-I poliomyelitis had become epidemic it was decided to offer type-II attenuated live vaccine to children aged three months to ten years. No type-II poliomyelitis had occurred since April, 1956. The hope was that type II would interfere with type-I multiplication and possibly give some heterologous protection against type I. 198,965 received the vaccine, remained " perfectly fit and afebrile, and continued a normal life ". The strain spread among 300,000 other children under 10. One child developed type-II paralytic poliomyelitis. It is possible this child got his infection from Johore Bahra, the neighbouring town, where type-II strains were common. Seven months after the last doses of type-II no other type-II poliomyelitis occurred. 7 cases of type I occurred among the vaccinated, whereas 46 was the expected number. 300,000 received no oral vaccine, but many may have been infected from those who received vaccine. 179 paralytic type-I cases occurred among these—an incidence of 60 per 100,000 compared with 3 per 100,000 among the orally vaccinated.

Dr. SABIN said if the opportunity came again he would choose type-I attenuated vaccine in preference to type II in similar circumstances.

Dr. V. SKOVRANEK (Czechoslovakia) said 242,556 children (58% of this age-group) had been vaccinated with three doses of Salk's vaccine, and that 143,377 had been vaccinated with Sabin's type I, 127,290 with type III, and 114,510 with type II. Many received more than one type. He concluded that the vaccine was safe, that antibodies were formed in a very high proportion of vaccinated persons, and that if epidemiological observations proved its effectiveness, Sabin's vaccine gave hope of complete eradication of poliovirus from the human population.

The principal discussion centred on whether live vaccine should be given alone or after preliminary vaccination with Salk's vaccine. The Czechoslovakian investigators had clearly shown that vaccination with Salk inactivated vaccine in no way interfered with the production of antibodies by Sabin's vaccine.

Dr. S. GARD (Sweden) thought that Sabin's vaccine should be given as a reactivator of immunisation to children already given Salk vaccine, but Sabin was emphatic that if anyone did not trust his vaccine without preliminary use of Salk's vaccine, then it should not be used.

Dr. BAUER (U.S.A.), speaking of experiences in Minnesota, said that Salk vaccine had been discouraged but Sabin's vaccine had now been used on a large scale, and he was emphatic that it was safe and preliminary use of Salk vaccine undesirable. He said that giving the three types together appeared satisfactory in adults, but in children three single doses were better, usually given in the order II, I, and III.

Dr. T. S. L. BESWICK (England) discussed the antibody response to a third dose of poliomyelitis vaccine. Two of the vaccines were made in Canada, two in the U.S., and the five others were British. Schoolboys aged 13 to 19 with no antibodies were used and tests were made after the usual two injections. Little or no response to type I occurred in a high proportion. The third doses often produced disappointing results against type I and better results against type II and III. Four vaccines which were used would no longer be acceptable for use in the U.K. Manufacturers were urged to produce better vaccines with more antigenic type-I power. Unless this happened formalin-inactivated vaccine would lose its present place in prophylaxis.

Non-vaccine Problems

Dr. H. FLAMM (Austria), discussing prenatal infection with poliomyelitis, said that poliomyelitis in early pregnancy could affect the embryo, and compared it to rubella. If poliomyelitis attacked pregnant women the intrauterine death-rate of the embryo in the first three months of pregnancy was very high (47%). Premature birth occurred in 10% of those attacked in the first, 17% in those attacked in the second, and 9% of those attacked in the third trimester. Abnormalities were similar to those associated with German measles.

A paper by the late Dr. D. H. GEFFEN said that in 1950 in England and Wales there were 82 notified cases of poliomyelitis in children under six months, of whom 77 were paralysed. Mortality was 23% and increased as age diminished. Of the 78 survivors, 30 were severely paralysed and only two made a complete recovery. These alarming figures were not repeated but in the next six years 174 cases occurred of which 135 were paralysed. The 135 under six months who were paralysed compared with 9350 cases of paralysis in children of under 15 years shows that paralysis under six months is sufficiently important to demand whatever prevention is possible. He concluded that as immunisation with a killed vaccine was largely ineffective before the age of six months, expectant mothers should be immunised to protect themselves during the time of increased risk in order to pass on immunity to their newborn babies. Much of this was lost in the first three months and immunisation with a live vaccine seemed possible and in need of trial.

Dr. W. H. KELLEHER (England) called attention to the increased excretion of calcium and advised, as Sweet had done, the avoidance of catheterisation if possible, the giving of antibiotic as long as catheterisation was needed, bladder irrigation with Suby's solution, a high fluid intake, and possibly androgens. Rocking beds, a low calcium diet, and salicylates were of doubtful value.

Public Health

Current Questions

SEVERAL important reports from commissions, committees, and working parties have lately contained recommendations which may alter the pattern of the public-health services. In his presidential address to the Society of Medical Officers of Health on Sept. 25, Dr. J. Stevenson Logan discussed the implications of some of these proposals. The tripartite structure of the National Health Service, for instance, had been criticised in the Cranbrook report and elsewhere; but for the M.O.H. unification of the three branches might be fraught with "some promise and much danger". To become a junior branch of a larger organisation was not attractive to those who had enjoyed the relative freedom and enhanced efficiency of smaller organisations. Again it was often said that the new Mental Health Act offered many new opportunities; but opportunity had in fact existed since the N.H.S. began, yet little use had been made of it. Nor did Dr. Logan feel sanguine about finance or confident that willing authorities would be protected against the inertia of neighbours.

The success of most of the new proposals would depend largely on the backing of adequate welfare services, and, though the society believed that public health was good for welfare, Dr. Logan was doubtful whether the converse would prove true. The Younghusband Working Party saw health visitors and social workers providing a complementary service, and this might be the relationship of many M.O.H.s to welfare officers in the future. He thought the society should be careful about their reception of the Younghusband report and judicious as to how far they supported the claims of the health visitor, who, in Prof. R. C. Wofinden's phrase, "has yet to decide whether she is to be more medical or more social".

Jury Condemns Arsenical Sprays

After an inquest [1] at Bromyard, Herefordshire, into the death of a 38-year-old woman who had drunk arsenic-contaminated water at her home on a farm,[2] the jury declared that "these arsenical sprays should be prohibited altogether". A detective-inspector said that when he tested the farm equipment used for preparing the arsenical potato spray he found that the pump which drew water from the supply tank into the spray tank was faulty and allowed a flow-back into the main house supply at a rate of $1\frac{1}{2}$ gallons every seven minutes. The house supply tank contained 180 parts per million of arsenic (the safe standard is 0·05 p.p.m.). The farmer said the sprayer had been in use for seven years. He was fully aware of the dangers of the spray and took every precaution. He agreed that some of the spray had got into the house tank through a faulty valve. A pathologist said that the woman had died from "inflammation of the heart valves which might have been aggravated by arsenical poisoning". She might have survived but for the poisoning. A verdict of death by misadventure was recorded.

On Monday Fisons Ltd., of Felixstowe, manufacturers of agricultural fertilisers, announced that they are withdrawing all arsenical crop spray already distributed and that no more spray will be manufactured or distributed by them.[3] The spray ('Foliatox') is a mixture of sodium and potassium arsenites. All distributed supplies in this country will be taken back by Fisons by rail and road, and they hope to complete the withdrawal by Nov. 1. Their statement adds: "It is realised that this decision may cause some inconvenience to the potato growers, but to minimise these difficulties every effort is being made to increase Fisons' contract acid spray service for the burning off of potato haulms."

1. *Times*, Oct. 3, 1959.
2. See *Lancet*, Sept. 26, 1959, p. 458.
3. *Times*. Oct. 6, 1959.

Infectious Diseases in England and Wales

Disease	Week ended September			
	5	12	19	26*
Diphtheria	2	6	5	6
Dysentery	387	415	449	529
Encephalitis:				
Infective	4	6	10	3
Postinfectious	..	1	1	..
Food-poisoning	415	292	293	343
Measles, excluding rubella	1249	855	686	687
Meningococcal infection	13	6	20	17
Ophthalmia neonatorum	29	19	28	29
Paratyphoid fever	42	20	14	18
Pneumonia, primary or influenzal	101	107	132	132
Poliomyelitis:				
Paralytic	26	26	19	22
Non-paralytic	18	12	14	13
Puerperal pyrexia	180	221	215	187
Scarlet fever	248	303	402	531
Smallpox	..	..	..	..
Tuberculosis:				
Respiratory	378	424	366	440
Meninges and C.N.S.	9	4	6	7
Other	43	50	53	41
Typhoid fever	6	9	9	4
Whooping-cough	873	696	718	784

* Not including late returns.

Poisoning by Insecticide in Barley

During the afternoon of Sunday, Sept. 6, a child was admitted to the Civil General Hospital, Singapore, with symptoms of abdominal pain and vomiting. Before 9.30 P.M. a further 9 children were admitted to hospital with similar symptoms. All were seriously ill, and 2 died. Clinical examination suggested that an anti-cholinesterase was the cause of the illness, and barley-water was quickly implicated as the cause. The parents accompanying the children to hospital came to a similar conclusion among themselves. In all, 23 Chinese children were admitted, and 6 died. 2 other children were dead on arrival at hospital, apparently from the same cause.

Two or three hours after drinking barley-water the children felt ill, were seized with a gripping (but not gripeing) abdominal pain, vomited, sweated, and rapidly became prostrate and passed into coma. Excessive salivation occurred and this was followed by pulmonary œdema about two hours after the onset of symptoms. Pupils did not constrict until after the onset of pulmonary œdema. The administration of large doses of atropine caused dramatic improvement.

Barley-water, made by boiling barley in water, is a very popular drink with Chinese. The severity of the symptoms seemed to be correlated to the amount of barley-water drunk. Symptoms were worse where the grains of barley had been eaten.

The outbreak was confined to a small area of Singapore, and by next morning sacks of barley had been recovered by the health department from two shops which had sold barley to the affected families. These sacks were part of a consignment of 400 sacks recently imported in a German ship. The consignment had been widely distributed through Singapore, the Federation of Malaya, and Sarawak; but all sacks were recovered, and after the initial outbreak no further cases occurred. Subsequently pharmacological experiments showed that the barley was contaminated with anti-cholinesterase of the organic phosphorus group, and chemical analysis showed that this was 'Parathion'. How the sacks became contaminated has not yet been discovered, but it seems that they were contaminated during shipment. Many of the sacks had been contaminated, some more heavily than others. Possibly organic phosphorus insecticides were shipped in the same hold, either at the same time as the barley or on some previous voyage. Inquiries are continuing.

The incident illustrates the danger of organic phosphorus insecticides and the care with which they must be handled.

Medicine and the Law

Home Secretary's Action in Podola Case

THE Home Secretary has referred the case of Guenther Fritz Podola to the Court of Criminal Appeal. Podola, who was recently sentenced to death for the capital murder of a policeman,[1] had decided not to appeal but had addressed a petition for the exercise of Her Majesty's mercy. The Home Secretary has the right when considering a petition for mercy to refer either the whole case or some special aspect of it to the Court of Criminal Appeal (see Section 19, Criminal Appeal Act, 1907).

Presumably the Home Secretary has referred the question of Podola's claim that he was unfit to plead in that he was suffering from hysterical amnesia. There is some doubt whether Podola could have appealed against the finding that he was fit to plead in view of a decision of the Court of Criminal Appeal in 1907. The Home Secretary's decision resolves this legal tangle and should enable the court to consider where the onus of proof lies in such cases and also of whether amnesia constitutes unfitness.

1. See *Lancet*, Oct. 3, 1959, p. 517.

In England Now

A Running Commentary by Peripatetic Correspondents

SHE is asking for an ambulance to carry her septic thumb to hospital for dressings. "It is three miles, Doctor, and the buses are so crowded." I am not listening, for although I am in England now, my mind is in another country, a month ago...

The car ferry is crossing a lonely stretch of water on its first trip of the day. It carries an American-type estate car, and in the flattened back is a wicker basket, $6^1/_2$ ft. long. Lying in the basket is a peasant girl, wrapped in blankets. It will jolt its way over the pre-macadam road down the opposite waterside, and some time in the late afternoon will deliver her to hospital. This morning, early, it met her with its basket, as far and as high as it could go. Her journey started yesterday, for she left her farmhouse on a horse, and rode all day over the mountain plateau. The diagnosis? Rheumatic fever. Even before she started this rugged journey, she ached in every joint....

"What did you say? An ambulance for your thumb?" Do we realise, in England now, how lucky we are?

* * *

It was my defective Latin really—or perhaps the uninspired teaching of my late mentor—that diverted my early steps from our more ancient universities to the relatively red bricks of London. At the time I didn't worry. London was much bigger and therefore better and I had been born there. And I never really grasped what I had missed until accident brought me an invitation to discuss something erudite with some don or other a few months ago. What an experience! A glory of green grass (feudally restricted to the elect), carved stonework, oak beams, and uniformed servants. Softened up by this, tea in the S.C.R. was almost a mystical experience; it would have sent an American tourist unconscious. Brass kettle sang on hob, old prints and period furniture surrounded us, Johnson's dictionary, calf-bound, stood alongside Crockford and other works of reference. A don sat reading *Le Figaro* and tea was served, perfect in every detail, in monogrammed silver. The whole thing was out of this world—and therein perhaps lay its weakness, for it seemed inappropriate to discuss anything more topical than antecedents to the Crimean campaign. Medieval church history, Greek drama, or Middle-Eastern ceramics would have fitted in, but psychology, criminology, sociology would not. After all they have no tradition—no wonder they find these places pretty stony ground. But it was good to have a glimpse of a famous university in its intellectual twilight. Maybe it won't enter this century until the beams are replaced by pre-stressed concrete, the stonework by chromium plating, and the S.C.R. turned into a cafeteria.

* * *

During a glorious summer, my most interesting case in this seaside practice has been the Man Who Felt Cold. He insisted on sleeping fully dressed, packed himself up with hot-water bottles and blankets, and although he never had chilblains in the winter, he certainly had them in August. Only after he lost the tips of three toes from frostbite did I discover that a crowded boarding-house had made him up a bed in the deep-freeze.

* * *

An advertisement inviting medical men to apply for places in an Australian Government expedition to the Antarctic states, reasonably enough, that applicants must be in robust health. And then slips in a casual note saying that "appendectomy is essential before sailing".

Well, now, we've all become accustomed to being pricked, scratched, X-rayed, and even finger-printed as a condition for permission to proceed to strange places; but it has taken the bold mind of a young and thriving nation to show us how pale and pusillanimous these measures have been. Of course, clearly, it would be awkward to have to do an appendectomy (or even an appendicectomy) in an igloo; and the difficulty would be sharpened in Antarctica by the absence of igloos. But it costs the tax-payer money if some incoming body has to

be appendectomised in England—and as for space ships. The obvious answer is for everyone to have the job done first wherever they are and before they go to wherever they hope to be. Let us older, stodgier people take the Australian hint, and frame forthwith a comprehensive list of health requirements to be fulfilled by all seeking licence to tread our green and sanitary hills. As a fringe member of the health corps I would suggest as obviously desirable inclusions:

Prefrontal lobotomy, to obviate the risk of having to treat some future anxiety state.

Splenectomy, thus reducing the chance of bleeding in motor accidents.

Gastrectomy, to safeguard the national stockpile of alkaline salts.

Pulmonectomy, to combat the rising incidence of bronchial carcinoma, and, indeed, to solve the whole problem.

An astute Minister for Health will soon see that the system could be applied with advantage not only to odd incomers, but also to the natives.

* * *

When our eight-year-old questioned me about the general election I tried to give him an all-round view, pointing out the pros and the cons of each party. But now he seems to think that a Labour Government will immediately demolish his school, brick by brick, and that the Conservatives will starve to death the old lady down the road who shouts at him for stealing her conkers. Both these occurrences would be so delightful that he cannot make up his mind which party he supports.

* * *

About the middle of the night, a Thing with fins
Came to reprove the Tutor for his sins,

began the scandalous Cambridge poem by Christopher Isherwood and Edward Upward. It is unlikely that the monster they had in mind was much like the latest American cars, but their huge useless fins are certainly a prominent feature—and perhaps a dangerous one. In a recent issue of a satirical magazine there appeared an account of some injuries likely to be caused by the novel features of today's American car—strangulation by power-operated windows, blows from a driver rotating in a swivel seat, and above all gashing and goring by the monstrous fins. But more sinister is the thought that one of these finned Things may contain a policeman in disguise. At least in the State of Connecticut the motorist can no longer exceed the speed-limit on the fine parkways comfortable in the knowledge that there is no police car in sight; for unmarked cars driven by plain-clothes cops (or " law-enforcement agents " as they now prefer to be called) are cruising seeking their prey. This may seem unfair, but at least it has cut down the accident-rate; moreover there are signs posted warning motorists that unmarked police cars are abroad—which seems sporting.

* * *

Lundy, with its population of under 20, has a remote and feudal atmosphere and is probably the least known of the islands of England. Although just visible from the mainland, its sense of remoteness is increased by its inaccessibility. Landings may be difficult or impossible for long periods when the wind is in the east. I have just spent six days there—three because I couldn't get off. All this, and its somewhat primitive facilities, make it a welcome refuge from the noise and fumes of London traffic. Before the first world war it was owned by the Rev. Hudson Heaven, who built its church and it was known as The Kingdom of Heaven. Many would feel that it still deserves this title today.

* * *

A Dialectical Dialogue

The tame pig said to the wild: "Oh, why
Won't you join us and gobble your fill?
What forest can vie with a hygienic sty
And lashings of sterilised swill?"
The wild pig replied with a snort: " My friend,
Your progress may prove Gadarene!
If you fancy your means justify your end,
Fatten up! I prefer to be lean."

Letters to the Editor

BEDS FOR CONFINEMENT

SIR,—I shall not be alone in deploring the present trends of thought about the future maternity services in this country. We have suffered a spate of pronouncements from Above, articles in the medical and lay Press, and speeches from all quarters giving reasons why all, or nearly all, mothers ought to be delivered in hospital. And now the pædiatricians (Sept. 26) have joined in with reasons why every baby should spend its first four days in hospital. As a very natural result, the public have come to regard a home confinement as something rather risky and adventurous and the domiciliary midwives and the service they offer as something definitely " second-best ". This is plainly unfair to the mother who cannot get into hospital, or who does not want to, and to the district midwives who must find it difficult to preserve their esprit-de-corps in such circumstances.

It is time that someone spoke up for a little reason and common sense in all this. If a little of the time and thought being expended on the matter was given to the far more satisfying and infinitely cheaper task of ensuring that domiciliary midwifery is made as safe, or safer, to both mother and child than delivery in hospital, everyone would benefit. Nearly every conclusion reached in the recent reports on different aspects of midwifery could honestly be prefaced by the words " In the present state of lack of coordination between the hospital and domiciliary midwifery services . . ." and we might as well face it. All over the country there are maternity beds filled with normal women with good homes whilst those with social difficulties cannot get in and there is trouble and delay in admitting emergencies. Seldom are the maternity facilities in an area coordinated and used to the best advantage of all and seldom do we find a system of booking in which " first-come-first-served " is not a predominant feature.

It is not difficult to coordinate the facilities of an area; but to do so the obstetrician in charge must be prepared to step down from the heights and spend some of his time at his desk and, together with the medical officer of health, institute and maintain a system of selection to which all, and that means all, applicants for maternity beds are subjected. So long as this system is run fairly, and is seen to be so run, and so long as appeals against the decisions made are given fair weight and beds are made immediately available (and this system will ensure that there are spare beds however meagre the facilities) whenever they are required and for whatever good reason, there has been in my experience no difficulty in gaining general acceptance.

Such a system has been worked for years in this area and it can be honestly said that, despite the most inadequate facilities in a rapidly growing town, no woman who has required a maternity bed for medical or social reasons has ever been refused and no emergency has ever been turned away. And because the hospital has never been in competition with the " district " but has rather been a partner, the latter has neither felt nor been regarded as inferior in any way and is consequently in good heart and has an excellent staff with little turnover.

Anyone interested to see how such a service can run is welcome to come to Swindon and we shall do our best to show them.

Maternity Hospital,
Swindon, Wilts. GUY ROWORTH.

SIR,—May I support your annotation of Sept. 19 and press that the principle be accepted—that early discharge home after hospital confinement is the *right* way of caring for some patients. For example, consider the woman with a history of postpartum hæmorrhage who has a young child, a good home, and home help. Clearly in her case it is important that she be confined in hospital where all facilities are readily available for the prevention (intravenous ergometrine with the birth of the anterior shoulder) and treatment of any hæmorrhage that may recur. Usually of course the delivery is normal and uneventful when surely early discharge is the thing for her. In Sheffield we arrange this for some patients and, provided the arrangements are carefully made, much is gained: more would be gained if the Minister of Health would allow such patients part of the home-confinement grant. There is another argument in favour of this policy —namely, that unless we provide a service of this kind some women who, all are agreed, should be delivered in hospital will insist on staying at home with all the risk involved.

One of the real difficulties (apart from the relevant recommendations of the Cranbrook Committee, which admittedly were qualified) is that the Central Midwives Board's rules in regard to the training of midwives have made early discharge very difficult if not actually impossible to put into widespread practice. Now that the advantages of selected early discharge are so widely acknowledged (and by the midwives themselves) could not the Central Midwives Board admit the rightness of early discharge for some women and thereby do something to break down the barriers between the hospital and domiciliary midwife to the benefit of both?

The shortage of midwives has now been publicly proclaimed on television ('Panorama') and recruitment may improve, but until it does the critical years ahead with an increasing birth-rate and many more young persons growing up will only be met by the early discharge home of those patients who are fit and willing, and whose home conditions are suitable.

Department of Obstetrics and Gynæcology, Jessop Hospital for Women, Sheffield. C. SCOTT RUSSELL.

SIR,—The letters of Dr. Scott and Dr. Beryl Corner in your issue of Sept. 26 raise very interesting points in this most difficult problem of maternity beds.

Dr. Corner proposes a stay in hospital of up to four days and that the training of midwives should be adjusted accordingly. She does not suggest how this could be accomplished; and would appear to overlook the fact that the home conditions of very many of the women are quite unsuitable for the care of the mother and babe at this stage.

What Dr. Scott appears to overlook in his anxiety to protect his clinic doctors and midwives is that the local authority in London will not permit its midwifery service to care for women who have had their babies in hospital until after the fourteenth day.

To square Dr. Corner's views with Dr. Scott's embargo is one of the problems which bedevil us all.

A. J. TASKER
Secretary,
Lewisham Group Hospital Management Committee.
Lewisham Hospital, London, S.E.13.

CRIME AND PUNISHMENT

SIR,—I was interested to note in the Dialogue of Sept. 26 the absence of retribution as a factor in punishment. Why is there such odium attached to retribution? Is it because many of us have become deterministic in our outlook? In which case we should take to heart Dr. Jackson's magnificent letter of Sept. 19 on Diminished Responsibility.

It may be because we are so ready to find excuses for criminals that crime is increasing. We assume that they are the victims of circumstances, genetic and environmental, and accordingly blame society for their crimes instead of laying the blame squarely on their shoulders. Our methods of punishment are definitely antiquated especially in a society with a rising standard of living and high wages. Incarceration for long periods in antiquated buildings, often in the close proximity of depraved social outcasts, with inadequate toilet or bathing facilities, causes us to commit a crime against the criminal, which is entirely out of harmony with the punishment he deserves. Higher fines, corporal punishment for violence against the person, apologies to the victim and to the court (i.e., society at large), adequate compensation to the victim and his relatives (even if this means paying higher wages for the work done in prison) are more humane than depriving a man of his liberty and the comfort of his family.

Hull. L. I. HARDY.

DEOXYRIBONUCLEIC ACID CONTENT OF HUMAN CARCINOMA CELLS

SIR,—We read with interest Professor Stich and his collaborators' communication (Sept. 19) in which they report their findings on the D.N.A. content of human carcinoma cells as measured by a microspectrophotometric technique. In contrast to benign polypi of the large intestine and stomach, they find that adenocarcinomas arising at these sites have greater amounts of D.N.A., corresponding to either hyperdiploid or near-tetraploid chromosome numbers, which as they mention are broadly similar to our earlier results on a variety of human malignant tumours.[1] They suggest that it may be possible to distinguish between benign and malignant tumours of some tissues on the basis of measurement of D.N.A. content of a small number of nuclei. This may be true; we should point out, however, that at several sites we have found occasional malignant tumours having a pattern of D.N.A. values indistinguishable from that of a normal (diploid) dividing tissue. Thus, in a series of 132 carcinomas of the cervix uteri and 33 of the corpus uteri, the individual tumours have been found to extend over a wide (approximately fourfold) ploidy range, including in both instances a few in the diploid region. Diploid tumours have also been found in the bladder and breast. We feel, therefore, that in the present state of knowledge caution should be exercised before a tumour be regarded as benign on the basis of a "normal" D.N.A. content. Although these "diploid" tumours have, within the limits of our technique, a normal D.N.A. content, it is still of course possible that they may exhibit small changes from the normal in their chromosome complement.

We have in fact previously reported[1] a case of carcinoma of the cervix in which the D.N.A. content was found to be within normal limits but the chromosome number was hypodiploid. Other cases that we have found of lack of proportionality between D.N.A. content and chromosome number,[2] not unexpected in view of the gross structural changes as well as loss or gain of whole chromosomes that are found in the karyotype of malignant cells, lend support to the view that "diploid" tumours may not necessarily have a normal chromosome complement.

1. Atkin, N. B., Richards, B. M. *Brit. J. Cancer*, 1956, **10**, 769.
2. Richards, B. M., Atkin, N. B. *Acta Uni. int. Cancr.* (in the press).

It may be of interest that we have just completed two further communications on the subject of the D.N.A. content of human tumours in relation to their clinical and pathological features and response to radiation therapy, which we hope will be published shortly.

Department of Cancer Research, Mount Vernon Hospital, Northwood, Middlesex. N. B. ATKIN.
M.R.C. Biophysics Research Unit, King's College, London, W.C.2. B. M. RICHARDS.

HÆMOPHILIA A IN A "GIRL" WITH MALE SEX-CHROMATIN PATTERN

SIR,—In the case reported in *The Lancet* by Professor Waldenström and his colleagues (Sept. 5) the possibility of combined deficiency of antihæmophilic globulin and capillary defect (a variety of von Willebrand's syndrome) was not excluded. Neither the fragility nor the morphology of the capillaries were examined. Furthermore, Bridge anticoagulant,[1] which is now used as a criterion for the diagnosis of true hæmophilia,[2 3] was not tested for.

Department of Hæmatology, The Royal Infirmary, Manchester, 13. F. NOUR-ELDIN.

OSTEOCHONDRODYSTROPHY

SIR,—In their account of a family affected by osteochondrodystrophy, Dr. Lomas and Dr. Boyle (Sept. 26) state that the disease was inherited as a mendelian recessive. Study of the family tree shows inheritance as a mendelian dominant.

Incomplete penetrance is suggested by the unexamined but probably affected individual in the third generation, born of a normal father. However, if it is assumed that the disease is inherited as a fully penetrant mendelian dominant, and that the disease does not affect fertility, then when 100% of the first generation are affected it is to be expected that 50% of the second generation and 25% of the third generation will be affected. These figures are close to the 53% and 22% found by the authors.

A fundamental issue is raised by the observation that "none of those with minor involvement transmitted the condition, which thus tended to die out in succeeding generations." This would make osteochondrodystrophy unique amongst hereditary disorders, so an alternative explanation may perhaps prove more acceptable: if some members of the third generation are still young they may yet manifest the disease; alternatively, if the disease is not fully penetrant, some apparently healthy members of the third generation may yet have affected children.

It would be of great interest for a further report on this family to be published in a few years' time.

Hillingdon Hospital, Uxbridge, Middlesex. D. WISE.

SIR,—Dr. Lomas' and Dr. Boyle's family with osteochondrodystrophy is an interesting one, but their account of it may create confusion.

(1) The condition cannot be due to a "recessive factor". The odds against 11 "markedly affected" individuals having each met and married one of the rare carriers of the gene are astronomical.

(2) A dominant gene would explain the pedigree very well, except for the curious observation that all 16 children of "slightly affected" individuals are normal. The evidence for a dominant gene in this family is otherwise so strong that it is likely that the authors have misdiagnosed some of the "slightly affected" or some of their children.

(3) While the nomenclature is not important, the patients in this family differ substantially, both in the radiographs shown and in their obvious reproductive fitness, from the truly autosomal recessive form of osteochondrodystrophy, first described by Morquio, and by Brailsford, and many times since. They are perhaps closer to the single family described by Jacobsen, but here a sex-linked recessive gene is concerned and no radiographs now exist of this family for comparison.

Have Dr. Lomas and Dr. Boyle compared their patients with those in other families, showing forms of osteochondrodystrophy due to dominant genes? Some of those, given rightly or wrongly the name of "multiple epiphysial dysplasia" with affected spines, show a resemblance. Radiographs of hips and ankles, not illustrated in the article, would be helpful in making comparisons.

Orpington, Kent. C. O. CARTER.

SARCOIDOSIS AND TUBERCULIN REACTION

SIR,—Surely Dr. Edelston (Sept. 26) is wrong in assuming that a positive tuberculin test excludes a diagnosis of sarcoidosis. It is also surprising to learn that he has never seen a case of sarcoidosis with a positive Mantoux reaction.

During the past two years, I have been able to observe several cases of proved sarcoidosis with a positive Mantoux test. Three of them were positive to a dilution of 1/1000, though the usual strength to evoke a positive response lay near 1/100. In all these cases, the diagnosis has been confirmed by scalene biopsy, Kveim test, and liver biopsy. In a recent paper, James[1] has also stressed this point. He found that 100 tuberculin units might be necessary to evoke a positive response in sarcoidosis. Moreover some patients with negative Mantoux reactions revealed sensitivity to depot tuberculin.[2] As many as 40% of his series had a positive reaction to tuberculin. A recent American textbook[3] even says "a positive reaction to tuberculin is of no value in excluding sarcoidosis." It is generally said that after steroid therapy the skin may react to the tuberculin but I have noticed a reverse phenomenon in one case.

I agree with other correspondents (Sept. 19) that Dr. Edelston's diagnosis of "thesaurosis" (Aug. 15) was based on flimsy ground.

London, N.4. SAMIR K. GUPTA.

EARLY DIAGNOSIS OF PREGNANCY

SIR,—Dr. Hobson's observations (Sept. 19) on the Hogben test are very sound, and this test must be regarded as the standard one. Your readers, however, might be interested in another simple method of reaching a diagnosis, using the cervical mucus, immediately after a missed period. This we have found a valuable precursor or adjunct to the Hogben test in cases where there is real clinical doubt and where the diagnosis is important.

Papanicolaou described how a drop of cervical mucus spread on a slide and left to dry, showed fern-like crystals under the low-power microscope. These crystals, which we have shown to be composed largely of simple salt, are present during the follicular phase of a cycle but absent in the luteal phase and in pregnancy. Thus in metropathia or stress amenorrhœa a single slide showing definite salt crystals gives a categorical diagnosis in a few minutes of non-pregnancy. Where no crystals are seen the patient may be pregnant, and the test is repeated 4 days after an injection of 10 mg. œstradiol. This has no effect on the pregnant but produces crystals in the non-pregnant. Zondek in Israel and we in Glasgow have used this method in over 300 cases and find it almost as reliable as the gonadotrophin tests and frequently more suitable.

1. Nour-Eldin, F., Wilkinson, J. F. *Brit. J. Hæmat.* 1958, **4**, 38.
2. Wilkinson, J. F., Nour-Eldin, F., Israëls, M. C. G. *Lancet*, 1958, ii, 115.
3. Israëls, M. C. G., Nour-Eldin, F., Wilkinson, J. F. *Postgrad. med. J.* 1959, **35**, 514.

1. James, D. G. *Quart. J. Med.*, 1959, **28**, 109.
2. James, D. G., Pepys, J. *Lancet*, 1956, i, 602.
3. Hinshaw, H. C., Garland, L. H. (editors). Diseases of the Chest; p. 561. Philadelphia, 1956.

The test is less valuable to the average busy practitioner since a vaginal speculum examination is required, but it can be carried out quickly and easily in any hospital unit.

Royal Samaritan Hospital for Women, Glasgow.

R. R. MACDONALD
A. SHARMAN.

PERCEPTUAL ISOLATION USING A SILENT ROOM

SIR,—As forecast by Dr. Black (Sept. 26), the silent room described by Dr. Smith and Mr. Lewty (Sept. 12) may well provide a useful means of increasing suggestibility. It is curious, however, that so little attention has been paid to this problem, and that the pharmacological possibilities are almost as unexplored as the physical limitation of perceptual experience. Acceptance of hypnosis in general is still very slow, and this is probably due to the fact that only 10–15% [1] of patients can actually reach the depth of trance necessary to make it a truly effective therapeutic weapon.

It was found by Goldie [2] that situations of acute stress raised the proportion of patients in whom successful analgesia could be induced by hypnosis to as much as 60%, implying that suggestibility increases in the face of danger or pain. It seemed to me that this may well be the result of biochemical change, and I am now trying to find a pharmacological agent which will satisfactorily increase the suggestibility of subjects known to be resistant to hypnosis. The preparations under investigation have been selected from the usual analeptics, hypnotics, tranquillisers, and analgesics used in general practice and psychiatry. It is also intended later to investigate the effect on suggestibility of different blood-levels of CO_2 and O_2.

No really significant findings are yet available as a result of this work, but meanwhile Dr. Smith and Mr. Lewty might care to see whether the triad of perceptual isolation, suggestion, and drugs is not in the end the most powerful hypnotic technique of all.

London, W.1. ADAM ROSENBLATT

THE INTERPRETATION OF CHROMOSOME COUNTS

SIR,—Your leading article entitled New Thoughts on Leukæmia (Sept. 25) stated, "Another important point to be borne in mind is that chromosome abnormalities may occur in other proliferative states in the bone-marrow. For instance, Ford et al. record that in one case of pernicious anæmia 35% of the mitotic cells had fewer than 46 chromosomes, and pernicious anæmia is not a malignant disease but a vitamin deficiency." This suggests that we interpreted the observed variation in the counts as evidence of real variation in chromosome number. In fact, the contrary is true.

Chromosome counts made on sternal-marrow biopsies from two cases of pernicious anæmia were reported in the paper quoted.[3] The recorded counts exhibit considerable variation, with a mode of 46 in both cases, an approximately symmetrical distribution in the one and a pronounced negative skewness in the other. Similar variation was also recorded in marrow taken from 12 more patients, including instances of other anæmic conditions, one case of polycythæmia vera, and two cases of leukæmia. The preparations used were our first essays with a new technique and were well below the standard attainable with animal material. In view of the errors involved we were at pains to discount the recorded variation and to argue that the data could not be interpreted as evidence of inconstancy of somatic chromosome number. I cannot, therefore, agree that the counts provide evidence for supposing that there may be true variation in chromosome number in either of these cases of pernicious anæmia.

It may be that it was the extensive variation in the counts recorded in our 1958 paper that have prevented some from accepting the evidence for mosaicism in cases of Turner's syndrome, mentioned in your third leading article in the same issue. Our recent preparations are, in general, much better, although still not the equal of those obtainable from experimental animals. Cells can be chosen where the fixing, staining, and dispersion of the chromosomes are good enough to ensure that errors of interpretation are rare, and often resolvable by matching the chromosomes in pairs. Errors of counting may still occur very occasionally, but a measure of objectivity is achieved by dividing the chromosomes into separate groups, counting and recording each group separately and then summing. In this way the bias in favour of arriving at an "expected number" is avoided. Nevertheless, in our more recent preparations few of the recorded counts depart from the standard somatic number of the individual, except in some leukæmic patients and a few instances interpreted as mosaics. In the latter the chromosome-count distribution was so different as to preclude the possibility of artefact.

This is not the place to argue the case further but I should point out that the bone-marrow observations from which mosaicism in cases of Turner's syndrome was inferred were made on patients other than those who provided the skin-biopsy specimens for culture. However, even if the bone-marrow and skin-culture examinations had been made on the same patients there would have been no conflict in the observations.

M.R.C. Radiobiological Research Unit, Harwell, Didcot, Berks. C. E. FORD.

DEATH AFTER FIRST TREATMENT WITH ELECTROPLEXY, THIOPENTONE, AND SUXETHONIUM BROMIDE

SIR,—The week before Dr. Campbell's letter (Sept. 19) appeared, a similar case occurred at this hospital.

A patient aged 39 was admitted after taking an overdose of sleeping tablets. She did not seem depressed, both when seen before admission and here. She complained of double vision and a banging in the head for about a month. She was thought to have diminished reflexes on the left side, and she was seen by a physician, who excluded an organic basis for her symptoms, even though her husband did not describe a picture of straightforward depression. In view of the suicidal attempt it was decided to treat the patient as an endogenous depression with atypical features.

On Sept. 16, 1959, after gr. $^1/_{100}$ atropine by injection, the patient was given 0·1 g. thiopentone and 50 mg. suxethonium bromide ('Brevidil E'). A well-modified fit was then induced with the E.C.T. machine, an airway inserted, and the patient artificially oxygenated until natural respiration returned. She was then moved on the same trolley to the ward and transferred to a bed to make room for the next E.C.T. patient.

Two more patients received E.C.T. and I went out of the E.C.T. room and was just washing my hands in the ward when the sister-in-charge told me that the patient had collapsed—about 10·45 A.M. Questioning subsequently established that the patient had been breathing spontaneously and was of good colour for at least ten minutes before her collapse. We established this by the observations not only of the nurses who stay by patients after E.C.T., but had it confirmed by the sister-in-charge who checks on all patients when returning one to the ward from the treatment room next to it, after their treatment. Thus, this case differs from Dr. Campbell's in that there appears to have been a delay before the catastrophe.

I found the patient profoundly collapsed and cyanosed. Natural respiration had ceased and radial pulses were absent. The patient had been turned on to her back and was being artificially respirated with oxygen, an airway being in place. I injected intravenously 2ml. of nikethamide without effect and repeated this until 6 ml. had been given. Vigorous attempts to

1. Lederman, E. I., Fordyce, C. Y., Stacy, T. E., Jr. *Maryland med. J.* 1958, **7**, 192.
2. Goldie, L. *Brit. med. J.* 1956, ii, 1340.
3. Ford, C. E., Jacobs, P. A., Lajtha, L. G. *Nature, Lond.* 1958, **181**, 1565.

revive the patient were instituted. The foot of the bed was raised and artificial respiration with oxygen was maintained. Methylamphetamine (30 mg.) was given intravenously and a few minutes later hydrocortisone (100 mg.) also intravenously.

At 11.30 a noradrenaline drip was put up (2 ml. in 500 ml. of normal saline). During all this time the blood-pressure was zero and the radial pulse came back weakly two or three times. There had been no sign of laryngeal spasm. The pulse at the apex varied between 120 and 160 per minute with occasional irregularities.

The help and advice of colleagues was available from about 11.20 onwards.

The patient began to develop pulmonary œdema and a mechanical sucker was used to remove fluid from the lungs. She showed no improvement. A consultant anæsthetist was satisfied that the measures so far taken should have been adequate, but suggested that aminophylline (0·5 g.) be given slowly. The anæsthetist was preparing for a bronchoscopy to aid clearing the lungs of fluid, when the patient's heart stopped (2.10 P.M.).

My main purpose in describing the resuscitative measures is to emphasise that in these very rare cases it is not simply a matter of profound circulatory collapse or the other kinds of collapses that occur after, say, any major anæsthetic, and I would be most interested to hear of anyone who has had experience of exhibiting potassium chloride and calcium gluconate where suxethonium was involved. Of course, in Foster's original article, suxamethonium was thought to be the agent responsible for a loss of muscle potassium.

The postmortem findings were only those of anoxia and no other lesion was discovered.

I would refer Dr. Campbell's attention to an article by Barker and May [1] on this subject.

West Park Hospital,
Epsom. ANDREW CROWCROFT.

SIR,—Dr. Campbell's letter of Sept. 19 prompts me to put on record two cases of prolonged apnœa which I have seen with this treatment and to comment on this rare complication.

A woman of 59, in good physical condition, was given atropine (gr. $^1/_{100}$) half an hour before treatment on July 31, 1956. Thiopentone (0·15 g.) was followed by suxethonium bromide (0·05 g.). Good relaxation and well-modified convulsion. Patient subsequently apnœic for 15 min. Abdominal respiration was maintained throughout. Continuous oxygen by mask, periodic artificial respiration. Nikethamide intravenously and aminophylline intramuscularly. Patient's colour and heart sounds were satisfactory throughout apnœic period. In view of the possible association of thiopentone with respiratory paralysis it was decided to repeat the treatment without anæsthetic and with 0·04 g. of suxethonium. Apnœa again occurred lasting 25 min. Recovery was uneventful.

On Sept. 29, 1959, a woman of 59, in satisfactory physical condition, had atropine (gr. $^1/_{100}$) half an hour before treatment. Thiopentone (0·15 g.) and suxethonium (0·05 g.). Well-modified convulsion. Apnœa developed and was complete for one hour, and partial for a further hour. Abdominal respiration was present but at periods during the first hour it was spasmodic and difficult to detect. During first hour, continuous oxygen with mask, artificial respiration for prolonged periods, nikethamide, methylamphetamine intravenously, and corticotrophin intramuscularly. At the end of this hour the patient's general condition was deteriorating. The colour was less good, pupils were becoming dilated, and heart sounds irregular. It was therefore decided to intubate the patient to ensure a better supply of oxygen. After this the colour improved, heart sounds became regular, and there was a slow emergence to full consciousness with return of spontaneous respiration over a period of an hour.

Succinylcholine compounds of which suxethonium bromide ('Brevedil E') is one are broken down by plasma-cholinesterase. The plasma-cholinesterase level in the first case was normal. Fisher and Bannister [1] also record a normal cholinesterase level in a patient who was apnœic for 5 minutes.

There is no clinical evidence that any form of treatment in these cases hastened the return of respiration. The patients should be adequately oxygenated throughout the period of apnœa by intubation if necessary until spontaneous respiration is resumed. With an impaired myocardium, as in Dr. Campbell's patient, the risk to life must, however, be increased.

Saxondale Hospital,
Radcliffe-on-Trent, Nottingham. T. J. N. BATES.

EFFECT OF NOISE ON ANIMALS

SIR,—Very large numbers of livestock of all species are now being carried by the international airlines, and this traffic is steadily increasing. Jet aircraft are not at present used, but they will be. In the meantime, livestock often encounter jet noises at close quarters at airports.

The airlines are in need of information and advice about the effects of high-frequency sounds on the various living creatures. I have been unable to discover any information on this subject, and would be most grateful for help from any of your readers.

Royal Society for the Prevention
of Cruelty to Animals,
Airport Hostel for Animals,
London Airport, Middlesex. STELLA ST. JOHN.

IMIPRAMINE

SIR,—We should like to draw your attention to some side-effects of imipramine ('Tofranil') which we have encountered. This drug is being used with some success in cases of depression, and favourable results have been reported in 50–70% of patients. Endogenous depressions seem to respond more favourably than reactive depressions. It has also been noticed that some patients who have not improved with E.C.T. have benefited from imipramine.

The side-effects which have been noted include malaise, dry mouth, thirst, difficulty with accommodation, insomnia, hypotension, and an increase of symptoms in those patients suffering from parkinsonism; in patients without previous neurological symptoms receiving high doses of imipramine, the development of fine tremor and muscular rigidity has been reported. The side-effects of imipramine are more likely to occur in those patients already suffering from neurological and psychic complications as the result of age or brain damage. In a comprehensive review Kuhn [2] details these side-effects and also notes variation in the patient's psychic state; thus general excitement was found combined with activation of the patient's psychic state, increased anxiety, hallucinations and delusions, or excitement with no particular content. Very rarely true mania developed. Similar states of excitement have been noted by other authors.

At Runwell Hospital, 29 patients have received courses of imipramine during the past seven months. The dosage and period of administration have varied greatly. The most common side-effects noted were dizziness, dry mouth, and difficulty with accommodation. These symptoms were transient, disappearing with continued therapy. Out of this total we should like to draw attention to 3 cases in which the neurological and psychic effects were of interest. The first patient took an overdose of imipramine as a means of suicide; the other 2 patients showed signs during the ordinary course of therapy.

1. *J. ment. Sci.* 1959, **105**, 496.

1. *J. ment. Sci.* 1953, **99**, 417, 796.
2. Kuhn, R. *Schweiz. med. Wschr.* 1957, **87**, 1135.

CASE 1.—Aged 32. A reactive depression in a high-grade mental defective. On July 10, 1959, we commenced a course of imipramine, 50 mg. thrice daily, increasing to 75 mg. thrice daily on July 12, and to 100 mg. four times daily on July 14.

On July 24, while at home on leave, at about 12.30 P.M. he took 32 tablets of 25 mg. each. The duly authorised officer, who was called by the patient's mother, reported that the patient was noisy and excitable, and calmed down only while in the ambulance during return to hospital. He arrived at about 4 P.M. He was very apprehensive, his face was expressionless. There was cogwheel-like rigidity of the arms. The systolic blood-pressure was 150 mm. Hg, but the diastolic could not be measured (this being checked by three observers). The pulse was 130 per minute, of good volume, and regular. Heart-sounds normal, no murmurs. Respiration 22. Temperature 98°.

At about 8.15 P.M. the patient again became very noisy and aggressive; he attacked two male nurses violently, and needed to be restrained.

At 8.40 P.M. myoclonic movements were observed, culminating in grand mal. After recovering from this he again became very excitable and was given amylobarbitone sodium 0·5 g. intravenously. At 1.30 A.M. he again became restless, and was given amylobarbitone sodium 0·5 g. by intramuscular injection.

The patient was on an hourly blood-pressure and pulse chart, and the diastolic pressure became measurable for the first time (80 mm. Hg) at 7.30 A.M. on July 25, the systolic being 130. This has remained fairly constant since. An electroencephalogram was performed at 12.30 P.M. on the same day by Dr. J. N. Margerison, who reported that there was no evidence of epilepsy or cerebral tumour, and to all intents and purposes the record was normal.

This man would now appear to have made a complete recovery from the above episode.

CASE 2.—Age 75. An arteriosclerotic dementia with depression, mild parkinsonism, and an old left hemiparesis.

Imipramine 25 mg. twice daily was increased to 50 mg. four times a day by Feb. 4, 1959.

On Feb. 7 the patient had a complete reversal of symptoms, talking, singing loudly, and generally overactive. These symptoms persisted, and the imipramine was reduced to 50 mg. thrice daily on Feb. 17. By Feb. 22 it was noted that while the patient was more alert his parkinsonism had become more pronounced, and he was unable to walk unaided or dress himself.

On the morning of March 7 he became excitable and was returned to bed. At noon generalised myoclonus was noted (the imipramine was then discontinued). The myoclonus persisted for a further 24 hours, and he has since gradually reverted to his pre-treatment state.

CASE 3.—A man of 71 suffering from a severe depression. Began a course of imipramine on Feb. 11, 1959, with 25 mg. twice daily, increasing in steps to 50 mg. four times daily on Feb. 17. From Feb. 15 it was noted that his gait was becoming very unsteady, and by Feb. 20, when imipramine was discontinued, he was unable to walk, had to be spoon-fed because of severe tremor, and his wife was becoming alarmed about his condition. There was a gradual recovery and by Feb. 28 he was again fully mobile.

Runwell Hospital, Wickford, Essex. GODFREY BROOKE
J. R. C. WEATHERLY.

NORMAL PSYCHOLOGY IN THE PRECLINICAL CURRICULUM

SIR,—Dr. Bourne's article of Aug. 29 prompts me to relate an experience of my own.

During the late war the preclinical students of the Middlesex Hospital Medical School were evacuated to Leeds, when I made the acquaintance of the late Prof. Samson Wright. He invited me to give a course of lectures on normal medical psychology, parallel with the lectures in physiology. The lectures were not compulsory, and there were no questions in the examination, yet they were very well attended, amongst others by Samson Wright himself, who sat in the front row and asked many pertinent questions in the discussion after the lecture.

After their return to London I had a letter from the secretary of the representative student body. He had been asked to say how much the lectures had been valued. At least it had made them appreciate, he wrote, " some of the differences between a human being and a decerebrate cat ".

As an unsolicited testimonial it is one of my prized possessions. It is also instructive in showing the students' interest in properly presented *medical* psychology, even in those days.

Leeds. H. EDELSTON.

ÆTIOLOGY OF PICA

SIR,—I read with great interest your annotation of Sept. 5. I have been interested in pica for a long time and I think this symptom depends entirely on sideropenia.[1]

I have seen about a hundred patients with this symptom and all of them had sideropenia. Most of them also had anæmia but the pica was observed in a few patients with normal hæmoglobins. All patients however, had a low serum-iron level. Most of them were women, but I have seen a few men who had undergone gastric resection or were blood-donors.

When treated with iron in adequate doses all patients lost their pica (about a hundred cases have been followed-up so far). This distressing symptom usually disappears in less than a fortnight, which is earlier than the anæmia.

County Central Hospital, Oerebro, Sweden. OLOF CARLANDER

THE ÆTIOLOGY OF LEUKÆMIAS

SIR,—The theory of the special evil within every " cancer cell " has again been affirmed by Dr. Laws (Oct. 3). We are used to this and it would not alone have provoked me to comment, but his attack on Dr. Schöyer for indulging in a type of thinking " which seriously inhibits much cancer research today " cannot be allowed to pass.

There have been, and there are, many clinicians and pathologists who do not " know " that " the cancer cell " is different from " the normal cell " or that it passes these differences on to its descendants in the processes of senescence and dedifferentiation in any fundamentally altered manner from that in which a normal cell hands on its line of progress in the processes of development and differentiation. So far from ideas like those of Dr. Schöyer's being inhibitory, they are, on the contrary, a much needed stimulus to help us break through the unproductive, fixed, ideas which have obstructed progress for so long. Perhaps that curious world of transplanted tumours in pure-strain laboratory animals in which so many cancer workers live has been responsible for their stagnation. There is no human counterpart to the perpetuation, by continuous rejuvenation in the host, of a metastatic tumour in what is virtually a single individual displaying no primary disturbance of growth pattern in its own tissues which is the very essence of neoplasia. These experiments seem to have concentrated the minds of research-workers on tumour cells, instead of on that dynamic balance of tissue growth and differentiation which is the basis of the development and maintenance of living organisms.

Instead of attacking those who, by thinking in terms of disturbances of normal biological behaviour, may get us out of this rut, research-workers who cling to the theory of the single, specific, intracellular heritable, cancerous change in all " cancer cells " should provide an interpretation of some of the facts which have for so long

1. *Svenska Läkartidn.* 1958, **55**, 387.

appeared to invalidate any such belief. We should like to know what they mean by "a cancer cell" in terms of our only definitions of neoplasms which are confined to descriptions of the behaviour of cell groups, of the long prediagnostic periods of gradual tissue change in growth habit which leads to neoplasia, of the lack of any definite borderline between "benign" and "malignant" characters in groups of abnormally behaving cells, of the progression which takes place in several behaviour patterns after tumour formation has become established, of multicentric origin, of spontaneous regression, of conditional persistence, of hormone dependence, and of the failure to demonstrate consistent physical or chemical differences between actively growing tumour cells and either similar cells involved in regeneration or those embryonal cells from which they were derived. We would also like an explanation of why we need to invoke one special intracellular, heritable change to account for dedifferentiation and overgrowth when we do not seem to need one to account for differentiation and development, regeneration, and repair.

Let us not discourage people like Dr. Schöyer who produce new explanations more in keeping with clinical observation for us to disprove on our way towards a better understanding. On the contrary let us decide to look much more critically at those things which "we already know", especially when they appear to be at variance with so much of our experience.

Royal Marsden Hospital,
London, S.W.3. D. W. SMITHERS.

SIR,—I should like to reply briefly to Dr. Laws.

I never asserted that increased rate of cell division was synonymous with autonomous growth. On the contrary I tried to make it clear that damage by external agents to genes containing the faculty of sensitivity to inhibition is part of a more extensive injury to the cells' genetic material. What results is altered cells that have lost a number of characters, which we are accustomed to call "normal", such as "those cellular mechanisms which normally maintain a regular relationship between the cells of an organ or tissue, &c."

I am not so sure as Dr. Laws that "an increased rate of division in the abnormal cells of a cancer is a prerequisite for the display of the other characters of those cells"; in my opinion those other characters, "which give the cancer its invasiveness, its capacity to metastasise, &c.", arise and are caused simultaneously by "the more extensive injury". The capacity to metastasise, for example, may at least partly depend on the well-known changes in the surface properties that lead to the lack of intercellular adhesions in cancer cells.

Gorinchem,
The Netherlands. N. H. D. SCHÖYER.

CHRISTMAS GIFTS FUND

SIR,—I shall be very grateful if you will spare space for me to remind your readers that Christmas will be coming round again soon, and to ask them to give a kind thought and a generous gift to the Christmas Gifts Fund organised by the Royal Medical Benevolent Fund.

To receive a gift at Christmas time is a joy to everyone, but particularly to those who are lonely or in need. To none is a gift more welcome than to those who have fallen on hard times.

Our beneficiaries include colleagues who have met with misfortune, and widows and children who are often in desperate need when their breadwinner has been taken before he was able to make provision for them. A gift at Christmas will enable them to enjoy some of the traditional good cheer of the season.

I ask your readers once again to give generously. Contributions marked "Christmas Gifts" should be sent to the Royal Medical Benevolent Fund, 37, St. George's Road, Wimbledon, London, S.W.19.

HENRY TIDY
President, Royal Medical Benevolent Fund.

Obituary

WILLIAM EDWARD GALLIE

M.D. Toronto, F.R.C.S., Hon. F.R.C.S.E.

Two years ago Professor Gallie chose to celebrate his seventy-fifth birthday in this country. He was accompanied by the Gallie Club (whose members were pleased to describe themselves as his "galley" slaves) on a surgical tour which included Edinburgh and Oxford, and a dinner was held in his honour in London at the Royal College of Surgeons, of which he was fellow, Moynihan lecturer, and gold medallist.

He was born in 1882 and qualified from the University of Toronto in 1903. When he was only 39 he was appointed surgeon-in-chief of the Hospital for Sick Children in Toronto, and in 1929 he was appointed to the chair of surgery at the University of Toronto. Under his guidance was started the first coordinated programme for the training of young surgeons in Canada. When he retired in 1949 he received a magnificent *Festschrift* from his old pupils. In 1941 he was elected president of the American College of Surgeons, and because of the war he held office for six strenuous years. In 1955 he was made an honorary fellow of the Edinburgh College. He died in Toronto on Sept. 25.

One of his English colleagues, C. M. P., writes:

"Gallie was one of the outstanding surgical personalities in the Western hemisphere of the past generation. In this country he was so acknowledged, I think, in virtue of his original contributions on the reaction of bone to injury and on fascial transplantation. The first subject was epitomised in association with D. E. Robinson in an article on repair of bone, published in the *British Journal of Surgery* in 1919. His study of fascia transplants and its several practical applications was carried out with A. B. Le Mesurier and was the subject of many papers between 1921 and 1937. Though he remained a general surgeon and was insistent on the avoidance of premature specialisation, his main interest in bone and joint surgery was perhaps derived from his early work under Royal Whitman and Clarence S. Carr, the latter of whom he followed in the chair of surgery at Toronto.

"In Canada and the States he was acclaimed as a leader in the organisation of the postgraduate education of the young surgeon which has over the years resulted in a great raising of the standard of surgery available over this vast area. The Gallie Club stands as memorial to this important influence.

"It may seem pretentious of one who only met Gallie at wide intervals over a period of years to attempt to size up his merits and the value of his contributions in a lifetime devoted to surgery. I would, however, say that despite the many academic honours which were showered on him, he remained modest, unassuming, and lovable. He was a big man, both physically and mentally. He was able to see visions and possessed the persistence and determination which enabled him to carry through a project which he had once clearly envisaged. He has left us after working a full term, having achieved as much as a man could hope for and has, moreover, left a band of associates and pupils inspired by his ideals to carry on the torch."

ABRAHAM FLEXNER

A.B. Johns Hopkins, A.M. Harvard, LL.D., Litt.D., hon. M.D. Berlin and Brussels

Though he held only honorary medical degrees, Dr. Abraham Flexner exercised, by virtue of his surveys and reports, a strong formative influence on medical education in this century.

He was born in Kentucky, sixth of the nine children of a Bohemian immigrant. One of his brothers was Simon Flexner, the bacteriologist, who later directed the Rockefeller Institute for Medical Research. After graduating in arts in 1886 Abraham Flexner taught in a high school for some years and then started his own school. The success of his methods, based on the principle of the minimum of restraint, won him academic recognition and the means to continue his own postgraduate education in Europe. His monograph on *The American College*, written in Heidelberg in 1908, led the Carnegie Foundation for the Advancement of Teaching to appoint him to investigate the medical schools of the United States and Canada, and his devastating report was published in 1910. Two years later he published another on *Medical Education in Europe*. Some years later he joined the general education board of the Rockefeller Foundation and took an important part in providing funds, as well as ideas, for the reorganisation of the American medical schools. He was also for some years director of the division of studies and medical education of the Carnegie Foundation. After he retired he spent some time in Oxford, where he gave the Rhodes and Taylorian lectures; and when he emerged from retirement in 1930 to create the Princeton Institute for Advanced Study, he modelled his new venture on All Souls, of which he was an associate member. He finally retired in 1939. He died on Sept. 21 at the age of 92.

Of Flexner's contribution to British medical education C. E. N. writes:

"Abraham Flexner has died at such a great age that to many people he must be little more than a name from the past. It is worth recalling him, because though he reaped unlimited praise for what he did for medical education in the United States and Canada, it is not so well known that he did a great deal to stimulate changes in medical education in England. His influence was established by the outspokenness with which, in his survey of medical schools in the United States and Canada in 1910, he said exactly what he thought in the most personal and abusive terms. He was right: a great many of the schools were a public scandal, and many of them simply closed their doors rather than face the criticism. As a result of this he was appointed to posts which gave him the opportunity to follow his destructive criticism with constructive action, and so high was the prestige he had earned that he was trusted by the financial powers to use money wisely.

"While all this was going on Flexner published, in 1912, his corresponding survey of medical education in Europe. The book fell into fertile soil because the Haldane Commission (1910-13) in England was deliberating on medical education, along with other aspects of university reform. Two streams met. Osler urged on the Haldane Commission the system he had learned from Welch at Johns Hopkins of 'hospital units'—the professor with his wards, laboratories, and assistants. Welch had seen this pattern when he was working in Germany under Cohnheim, and had introduced it at Johns Hopkins. Haldane admired some German methods, and was receptive to the idea. Flexner had been educated at Johns Hopkins, and by birth and training was deeply impressed by German educational methods; indeed, he even advocated some Teutonic notions which we would think undesirable.

"For a time, the effects of the Haldane report were held up by the first war, but afterwards the matter was taken up again, and by then Flexner had shown his constructive ability as an organiser, thinker, administrator, and collector of money. It was for this reason that his name carried so much weight in this country when, after the war, the first wholetime professorial medical units were being planned in England, an innovation which is now changing medical education. It may not be too much to say that Flexner's ideas contributed to making medical education in this country something of which we may one day have reason to be proud."

JOHN KIRK

M.B. Edin., F.R.C.S., F.R.C.S.E.

Prof. John Kirk, whose death on Sept. 26 we announced last week, did notable work as a missionary, an anatomist, and a teacher.

He was born in 1881 in an Edinburgh manse, and he was educated in that city at George Watson's College and at the university. After holding a house-appointment at the Mildmay Mission in London he went to China as a medical missionary in 1907. He continued his anatomical studies while he was resident medical officer at the New Zealand Presbyterian Mission Hospital at Canton, and during his first home leave in 1913–14 he took the F.R.C.S.E. In 1920 he visited Canada and the United States as a member of a delegation, financed by the Rockefeller Foundation, to organise support in these countries for the Canton Hospital as a centre of medical education in South China. On his second leave to England in 1921–22 he held a demonstratorship in anatomy in the University of Birmingham. When the new buildings at the Kung Yee Medical College, Canton, were opened in 1924, he was invited to organise and take charge of the department of anatomy, which was the first of its kind in South China. For six years he was a member of the council of medical education of the China Medical Association and held in turn the offices of chairman and president.

In 1928 he returned to England and joined the staff of University College as a demonstrator in anatomy. In 1930 he was also made responsible for the anatomy class preparing students for the primary F.R.C.S. examination, and for some years he was subdean of the faculty of medical science. In 1937 he was appointed to the Courtauld chair of anatomy at Middlesex Hospital. He retired in 1949 when he was elected professor emeritus. He was elected F.R.C.S. in 1952. He was visitor in anatomy examinations and of medical schools for the General Medical Council from 1953 to 1957.

G. G.-T., whose friendship with Kirk goes back a quarter of a century to his appointment to his chair, writes:

"From the period of Charles Bell in the 'forties of the last century Middlesex Hospital can boast of a high anatomical tradition, and from the first moment of his appointment John Kirk worthily upheld it. He had received his own early training in anatomy in the Edinburgh of William Turner and Dan Cunningham, but in China, whither his religious faith and missionary zeal had directed his footsteps, his anatomy became the handmaiden of his surgery: it was revivified in mid-life by his association with Elliot-Smith and Woollard at University College. His outlook remained that of the utilitarian rather than the academic anatomist, and it was to the practising doctor and the surgical aspirant that he especially addressed himself. As a teacher he was especially popular with candidates for the primary fellowship, particularly with the young surgeons from the Commonwealth, and it is probably true that along with Samson Wright, and his own anatomical predecessor, Tim Yeates, he did more than anyone to put Middlesex Hospital on the map of the surgical world. He lent a ready ear to any problem presented by a surgical colleague, and I believe that I may have been responsible for his interest in the choledocho-duodenal junction, a research in which we cooperated. His personal as well as his administrative qualities made him an ideal leader when the exigencies of war necessitated the removal of the Middlesex preclinical school to Leeds and to Bristol, while his complete integrity and fairness made him an excellent examiner.

"He was a charming gentleman, deeply religious, approachable by students, who respected, even worshipped him. Of no man is the Horatian line more true—*Integer vitæ scelerisque purus*".

Professor Kirk married in 1908 Norah Elizabeth Hughes, who survives him with two sons and a daughter.

Notes and News

MENTAL HEALTH ACT

ON Oct. 6 the Minister of Health brought into operation the part of this Act which permits the informal admission of patients to designated mental hospitals, registered hospitals, and licensed houses (S.I. [1959] no. 1676 C 13). Any patient who is not unwilling to be admitted and can suitably be treated without powers of detention may now be admitted to hospital in the same way as patients are admitted to general hospitals. Until a further Order is made the provisions for the admission of voluntary, temporary, and certified patients will remain in force side by side with the new power to admit patients informally. Informal admission will usually be arranged by the patient's own doctor, or by the hospital itself where the patient is attending the outpatient department. In his circular explaining the new arrangements to hospital authorities (H.M. [59] 92), the Minister asks that when a patient admitted in this way leaves hospital it should be " standard practice " to notify his family doctor and, with his consent, the local authority. No notification of admission or discharge need be made to the Board of Control or Ministry of Health. It will be some months before the Minister is able to bring into force the provisions of the Act dealing with patients who are subject to detention.

SOME MILITARY PERSPECTIVES

THIS year's D.G.'s Exercise—an annual " manœuvre " of the R.A.M.C.—began on Oct. 1 and it was given the title Exercise Medical Canaletto because, as the Director-General of the Army Medical Services, Sir ALEXANDER DRUMMOND, explained to the opening assembly, its object was to put a number of current problems into their correct perspective. And some of the subjects which came under scrutiny during the first day's sessions (held in London at the Royal Army Medical College, Millbank, in the presence of distinguished guests from home and abroad) were the initial treatment of burns, the hazards of nuclear radiation, and anæsthesia for large numbers of casualties.

The recurrent debate about what and what not to do as immediate treatment for burns was resumed in response to a new suggestion. Major A. V. FORAGE demonstrated how, after burned clothing had been cut away, the limb or body could be enclosed in a plastic bag, which would be retained in position until the patient reached a centre where restorative and other treatment could be undertaken. The hope was that such a container would reduce fluid loss by evaporation from the burned surface, as well as providing a rapidly applied non-stick dressing suitable for the conditions that might follow nuclear bombardment. But not everyone was convinced, and Mr. PATRICK CLARKSON pictured the plastic envelope rapidly becoming an abscess cavity.

Like most people, Lieut.-Colonel J. A. H. BROWN had nothing very cheerful to say about the hazards of nuclear radiation, and he made it plain that the " strategic " weapons of relatively small destructive power had altered the position considerably and thereby increased the radiation risk. The reduction in damage by blast and heat meant more likelihood of persons surviving the immediate explosion after exposure to high doses of gamma and neutron radiation. Neutrons were a relatively new hazard of nuclear explosions and it seemed likely that their principal action would be on the intestinal tract, producing a cholera-like syndrome, rather than on the bone-marrow. Prof. J. R. SQUIRE made a bold attack on the discouraging topic of how to treat radiation casualties. Among his tentative suggestions were the giving of potassium iodide by mouth in an attempt to protect the thyroid from ingested ^{131}I, the chilling of a limb that had been exposed while the rest of the body was sheltered, and the possible use of salicylates and cortisone in combating increased capillary permeability. The dose he suggested for gamma-globulin was 0·02 g. per kg. per week (the doses given to the Yugoslavians irradiated in last year's reactor accident [1] were, he thought, much too small). These and most of Professor Squire's other proposals were, as he put it, appropriate to what could be done for two patients by twenty doctors with all they needed: if large populations were exposed to nuclear attack, the position would be very different.

In trying to prepare for such a situation, Colonel K. F. STEPHENS saw a need for a simple means of safe anæsthesia for life-saving operations lasting about ten minutes. He suggested that a non-ignitable mixture of cyclopropane, oxygen, and nitrogen as an inhalation anæsthetic was the answer—a method first proposed by Dr. J. G. Bourne, of St. Thomas's Hospital, for dental operations. From Dr. Bourne's apparatus, a small portable anæsthetic machine had been evolved consisting of a facepiece, carbon-dioxide absorber, and rebreathing bag, which could be recharged from a pocket-size charging device. The bag was filled with 40% cyclopropane, 30% oxygen, and 30% nitrogen, delivered in one dose from a double-ended ' Sparklet ' bulb. This would provide five minutes' anæsthesia without danger of hypoxia or overdose; and the bag was then recharged if necessary. Colonel Stephens was optimistic about the use of this apparatus by largely unskilled persons with very slight knowledge of physiology; and he showed how, after only fifteen minutes' instruction, a dental hygienist had given a capable performance with this simple machine. Dr. BOURNE explained the advantages of cyclopropane for this purpose, but he did not persuade Dr. R. W. COPE, who thought this drug would disappear from hospitals in this country before many years were out. In an emergency he preferred to give intravenous thiopentone and a relaxant and maintain respiration by mouth-to-mouth breathing. But, as someone pointed out, this was hardly a method that could be taught to a dental hygienist or a swimming-bath instructor in ten or fifteen minutes—which was what Colonel Stephens was aiming for.

1. Jammet, H., et al. *Rev. franç. clin. biol.* 1959, **4**, 210.

AN APPEAL FROM EDINBURGH

THE University of Edinburgh has lately launched an appeal for £1 million to help it carry out a large building programme. Part of the cost will be borne by the University Grants Committee, but heavy contributions from the university itself will also be needed. Immediate plans include the completion of the extension of the medical school. The faculty of medicine is at present housed in the so-called New Medical Buildings erected in 1887 in Teviot Place, separated from the Royal Infirmary only by the Middle Meadow Walk, which is not open to vehicular traffic. The extension will be on the present site, and the new buildings will have their frontage on the north side of George Square. The first stage, at the north-west corner of the square, will soon be ready for use; but the whole extension is needed to accommodate the school of medicine adequately. Contributions may be earmarked for this extension, though other projects, such as the new university library, more halls of residence, common-rooms, and playing fields, will also benefit the medical faculty. Contributions should be sent to the Secretary to the University, Old College, South Bridge, Edinburgh 8.

WORLD FOOD AND AGRICULTURE

IN his annual report [1] the director-general of the Food and Agriculture Organisation of the United Nations sets out the statistics of world agriculture for 1958 with some provisional figures for 1959. The contrast between the highly developed countries and the less-developed ones remains acute. In North America the great advances in agricultural methods have led to the problem of disposing of abundant supplies: in the U.S.A. stocks of wheat now amount to 34·8 million tons, and of coarse grains to 63 million tons. The wheat surplus approximates to a whole annual harvest, and its size is increasing. This surplus has been the source of invaluable help to many less-developed countries in emergencies, but in the long run these countries can overcome their difficulties only by building up their own agriculture. In the Far East, in the Near East, and in Africa agriculture continues to expand—slowly. In most countries in

1. The State of Food and Agriculture 1959. F.A.O., Rome. Pp. 197. 10*s*. Obtainable from H.M. Stationery Office.

Asia the expansion is probably just keeping pace with the growth in population, but is insufficient to reduce the widespread malnutrition.

The report contains a detailed analysis of agricultural incomes in many countries. Farmers are often handicapped by unsatisfactory land tenure, lack of transport facilities, and poor arrangements for marketing. These factors may depress initiative on the farm and discourage the application of new knowledge, especially if most of the profits of any new venture go to the merchant or landlord. Unless the human and social, as well as the economic, conditions in which farmers live and work provide sufficient incentive, government programmes, demonstrations, and education will give disappointing results.

This report is valuable for its many tables setting out estimates of production of all crops in the major regions of the world, and also for a thoughtful essay discussing the reasons for the disappointing speed of development in so many countries.

A HYPNOTIST FINED

Norway's penal code imposes fines and up to 3 months in gaol for " whoever employs any means or procedures whereby he puts someone with his own consent into a state of hypnosis, weakness, loss of consciousness, or similar state "—a prohibition from which doctors, in search of knowledge or the cure of disease, are of course exempt. Lately this law has been invoked against a popular entertainer who, in giving a performance at the high school of a small town, enlivened his audience by willing four pupils to see, think, and do rather curious things: the sorcerer's rod flung on to the floor turned into a snake, an imaginary orchestra came into play, and various other absurdities were experienced by his subjects. For the prosecution a professor of psychology said that the performances could certainly prove mischievous, and the defendant was convicted of having induced positive and negative hallucinations. According to the account given by *Aftenposten* (June 19) he was fined Kr.100 with another Kr.100 for costs.

University of Durham

On Sept. 26 the D.P.M. was conferred on the following:
Jean Hayek, T. M. Maguire, Colin Protheroe.

College of General Practitioners

This College is holding a symposium at the Wellcome Building, Euston Road, London, N.W.1, on Sunday, Nov. 22, on prescribing and therapeutic trials in general practice. Accommodation is limited and those who wish to attend should write without delay to the secretary of the College, 41, Cadogan Gardens, London, S.W.3.

Epsom College

The council of this college will in June award two or more Henry Robinson scholarships.

Candidates, who must be the sons of doctors, must be under 14 and not less than 12 on Jan. 1, 1960. The normal maximum value is £250 per annum for a boarder and £150 for a dayboy; but the council have discretion to exceed these amounts. There is no means test for these scholarships. Candidates are eligible also for six open scholarships (£150 for boarders and £50 to £100 for dayboys). These are open to the sons of non-medical parents. Particulars may be had from the headmaster at the College, Epsom.

A New Faculty

A Faculty of the History of Medicine and Pharmacy has been founded under the auspices of the Society of Apothecaries of London.

The aim of the Faculty is to foster general interest in medical history, and to coordinate the work of medical historians with wider historical studies. Besides the annual Gideon de Lauvre oration, which will be delivered next year by Sir John Charles, it has endowment for two lectures which can be delivered in London or the provinces. A research fellowship, endowed by the Wellcome Trustees, is held at present by Mr. R. S. Roberts, a professional historian, who is working upon the early organisation of the drug trade from the 16th century. Announcements and reports of meetings will appear in the official organ of the Faculty, *Medical History*, which is published quarterly .

Further particulars can be had from Mr. Ernest Busby, clerk to the Society, Black Friars Lane, London, E.C.4.

Human Relationships in the Care of Mother and Baby

The Royal College of Midwives will hold a residential conference on this subject from March 28 to April 1 at St. Anne's College, Oxford. Application forms may be had from the education officer, the college, 15, Mansfield Street, London, W.1.

Society for the Study of Addiction

On Tuesday, Oct. 20, at 8 P.M., at 11, Chandos Street, London, W.1, there will be a symposium on the influence of drugs on literary imagination. The speakers will be Prof. Douglas Hubble, Miss Pamela Frankau, Mr. Christopher Mayhew, M.P., Dr. Emanuel Miller, and Dr. W. Linford Rees.

Abortion Law Reform Association

The annual general meeting of this Association will be held on Wednesday, Oct. 28, at 6.30 P.M., at Caxton Hall, Westminster, S.W.1. This will be followed at 7.15 P.M. by a public meeting at which Prof. W. C. W. Nixon and Miss D. M. Kerslake will speak on Safety Aspects of Medical Termination.

British Orthopædic Association

This Association will hold a postgraduate course in orthopædics on Thursday, Oct. 22, at the Royal College of Surgeons, Lincoln's Inn Fields, London, W.C.2. The speakers will be Dr. R. M. Mason, Mr. J. Bastow, Mr. W. D. Coltart, and Mr. T. M. Prossor. Tickets (10*s*.) may be had from the secretary of the Association, 47, Lincoln's Inn Fields, W.C.2.

Middlesex Hospital

At the annual dinner in London on Oct. 2 the toast of The Hospital and School was proposed by Prof. J. H. Woodger. Responding, Prof. B. W. Windeyer, the dean, said that the first phase of the rebuilding programme would be completed in six weeks, and Lord Astor had promised to open the new buildings in December. The remainder of the programme had been split into smaller instalments, and the first would begin in the middle of this month. In 1962 it was planned to start building a residential college, to be named Astor College, and this should be completed within two years. Of the £1$^1/_4$ million needed for these three phases, £$^1/_2$ million had been provided by the Court of London University and the University Grants Committee, and the rest by the school itself. Unfortunately the school's funds were now exhausted, and, despite several gifts and deeds of covenant by industry, Professor Windeyer could not forecast when the preclinical and clinical schools would be completed. Miss Barbara Lockley, the senior Broderip scholar, also replied to the toast.

Moynihan Chirurgical Club

Surgeons from many parts of the country and abroad gathered in Leeds Civic Hall to pay homage to the memory of Lord Moynihan at the 50th anniversary banquet of this club, which was founded by him to foster the progress of surgery, and to encourage friendship between surgeons at home and abroad.

Responding to the toast to his memory, his son, Lord Moynihan, recalled that before the club's foundation there was a striking lack of cohesion between members of the profession. By bringing surgeons into such a fraternity the profession benefited through the pooling of experience and the breaking down of prejudices. In this way, continued Lord Moynihan, quoting his father's own words, surgeons realised that they were " not competitors but comrades, each working with the other against the common enemy—disease ".

The toast of Berkeley Moynihan was proposed by Prof. Digby Chamberlain, president of the club, Mr. George Armitage, and Dr. Alton Ochsner, past president of the American College of Surgeons. The toast of The Club was proposed by Sir Ernest Finch. Mr. Robert Cooke was presented with a silver salver on his retirement after ten years as hon. secretary.

Representatives of other surgical clubs who had attended the two-day scientific meeting, on Sept. 24 and 25, which had preceded the banquet included Prof. Mallet Guy (Lyons), Prof. A. C. Brom (Leiden), Prof. E. Dahl-Iversen (Copenhagen), Prof. I. Boerema (Amsterdam), and Prof. Rudolf Geissendorfer (Frankfurt).

Development and Use of Modern Drugs

The University of Liverpool is holding a course of ten lectures on this subject on Tuesdays at 7.30 P.M., beginning on Oct. 13, at the Medical School, Ashton Street. The speakers will be Prof. Andrew Wilson, Dr. J. B. Roberts, Dr. G. F. Somers, and Dr. Harold Wilson. Tickets (£2 2s.) may be had from the director of extramural studies, 9, Abercromby Square, Liverpool, 7.

James Picker Foundation

This Foundation is this year offering advanced fellowships in academic radiology as well as research fellowships and scholar and research grants in that specialty. Applications for 1960–61 should be submitted by Dec. 15, and further details may be had from the Division of Medical Sciences—Room 411, National Academy of Sciences, National Research Council, 2101, Constitution Avenue, N.W., Washington 25, D.C.

Charing Cross Hospital Medical School

At the annual prizegiving and opening day on Oct. 1 Lord Inman, chairman of the school council, presided. The dean, Prof. W. J. Hamilton, recalled that this was the 38th anniversary of the day on which Lord Inman had originally taken up his duties as house governor of the hospital. Professor Hamilton reported that the union of Charing Cross Hospital, the Fulham, Fulham Maternity, and West London Hospitals had become effective from April 1, 1959, and that all concerned were now working amicably and with enthusiasm for the advancement and welfare of the newly combined hospitals. The number of beds for the new hospital at Fulham had finally been agreed at 800, and in addition, thanks to the efforts of the Vice-Chancellor of the University, Dr. Charles Harris, and its Principal, Sir Douglas Logan, the University Grants Committee had agreed to preclinical departments being included in the new medical school. In the past year's examinations 96% of the school entrants to the final M.B. had passed in medicine, 94% in surgery, and 87% in obstetrics and gynæcology. A generous benefaction had been promised to the school by the trustees of the Dan Mason Trust. The Dean referred with regret to the recent retirement of Mr. Eric Crook, and he welcomed in his place Mr. A. J. Harding Rains, the first professor of surgery.

In his inaugural address Lord Denning considered the relationship of medicine to religion, morality, and the law, and he spoke of the need for a background of moral and spiritual values to the practice of healing. He deplored the increased tendency to excuse all kinds of antisocial and criminal behaviour on psychiatric grounds.

The Homosexual Law Reform Society are distributing, on behalf of the Albany Trust, a pamphlet entitled *Some Questions and Answers about Homosexuality*. Some of the clear questions and concise factual answers deal with possible changes in the law as well as with the nature and extent of homosexuality. Copies (1s.) may be had from the society, rooms 27/29, 32, Shaftesbury Avenue, London, W.1.

Appointments

ABSON, E. P., M.B. Manc., F.R.C.S.: senior casualty officer, Royal South Hants Hospital, Southampton.
ARNOLD, PHILIP, M.D. Lond., M.R.C.P.: consultant physician, Bournemouth and East Dorset group of hospitals.
COLLIER, FLORENCE I., M.R.C.S.: medical superintendent, Church Missionary Society headquarters, London.
DAVIES, S. L., M.B. Wales, D.P.M.: senior assistant psychiatrist, Sheffield group of mental-deficiency hospitals and Middlewood Hospital, Sheffield.
DYER, J. V., M.B. Lond., D.P.H.: district M.O.H. and assistant M.O., Northamptonshire County Council (Burton Latimer, Corby, Desborough, Rothwell, and Kettering area).
GRANVILLE, CARMEL M., L.R.C.P.I.: assistant M.O.H. and school M.O., Dudley.
HODGSON, D. C., M.B. Lond., F.F.A. R.C.S.: consultant anæsthetist, United Oxford Hospitals.
JONES, J. K., L.M.S.S.A., D.P.H.: assistant M.O.H., Breconshire County Council.
MCGARITY, J. F., M.B. Durh., D.P.H.: assistant administrative M.O., Sheffield Regional Hospital Board.

Bristol Public-health Department:

ALDERSON, M. R., M.B. Lond., D.C.H.: assistant M.O.
CHESHAM, IRENE L., M.B. Lpool, D.P.H.: assistant M.O.
SUTCLIFFE, W. M., M.B. Leeds, D.I.H., D.P.H.: assistant M.O.

Diary of the Week

OCT. 11 TO 17

Monday, 12th

UNIVERSITY OF LONDON, Senate House, W.C.1
5.30 P.M. Dr. E. G. Holmes (Tanganyika): Aspects of Human Body Composition Related to Diet and to Some Endocrine Factors (First of three lectures.)
ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
2.30 P.M. Sir Clement Price Thomas: First Nuffield lecture.
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W.1
4 P.M. Dr. Denis Hill: The Role of Psychiatry in Medicine. (Bengue lecture.)
UNIVERSITY OF ST. ANDREWS
4 P.M. (Department of Medicine, Queen's College, Dundee.) Prof. D. M. Douglas: Surgical Treatment of Congenital Heart-disease.

Tuesday, 13th

ROYAL SOCIETY OF MEDICINE
8 P.M. *Psychiatry.* Dr. R. Ström-Olsen: Problems in the Study of Psychotic Illness. (Presidential address.)
BRITISH ASSOCIATION OF SPORT AND MEDICINE
5 P.M. (Arthur Stanley Institute, Peto Place, N.W.1.) Dr. J. M. Tanner, Dr. J. Fletcher: Results of Individual Research at the Empire Games.
MANCHESTER MEDICAL SOCIETY
8 P.M. (Staff House, University of Manchester.) *Surgery.* Mr. I. M. Orr: Surgical Problems of the Upper and Lower Extremities of the Œsophagus. (Presidential address.)
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5.15 P.M. (General Infirmary at Leeds.) Dr. J. M. Roberts: Use and Abuse of Tranquillisers.

Wednesday, 14th

ROYAL SOCIETY OF MEDICINE
4.30 P.M. *Physical Medicine.* Dr. Barbara Ansell, Dr. F. C. Rose, Dr. V. L. Steinberg: Neuropathies in Rheumatic Disease and Steroid Therapy.
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. Arthur Tickner: Biochemistry of Exfoliative Dermatitis.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. D. T. Carr: Pleural Fluid Glucose, with particular reference to Effusions in Rheumatoid Arthritis.
MANCHESTER MEDICAL SOCIETY
5 P.M. (Medical School, University of Manchester.) *Pathology.* Dr. P. J. L. Sequeira: Serology of Venereal Diseases.
UNIVERSITY OF ST. ANDREWS
2.30 P.M. (Department of Medicine, Queen's College, Dundee.) Professor Douglas: Investigation of the Peripheral Circulation in Limbs.

Thursday, 15th

UNIVERSITY OF LONDON
5.30 P.M. Dr. Holmes: Aspects of Human Body Composition. (Second of three lectures.)
ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, 26, Portland Place, W.1
7.30 P.M. Sir William MacArthur: Identification of Some Pestilences of the Past. (Presidential address.)
NUFFIELD ORTHOPÆDIC CENTRE, Wingfield-Morris Orthopædic Hospital, Oxford
8.30 P.M. Prof. C. Casuccio: Observations on So-called "Senile" Osteoporosis.
MANCHESTER MEDICAL SOCIETY
8 P.M. (Staff House, University of Manchester.) *Anæsthetics.* Dr. E. Falkner Hill: Fifty Years of Anæsthesia. (Presidential address.)
UNIVERSITY OF ST. ANDREWS
5 P.M. (Physiology Department, Queen's College, Dundee.) Mr. T. Holmes Sellors: Defects of the Atrial Septum.

Friday, 16th

UNIVERSITY OF LONDON
5.30 P.M. Dr. Holmes: Aspects of Human Body Composition. (Last of three lectures.)
ROYAL SOCIETY OF MEDICINE
5.30 P.M. *Epidemiology and Preventive Medicine.* Dr. J. T. Boyd: Influence of Meteorological Conditions on Mortality.
8.15 P.M. *Radiology.* (With Faculty of Radiologists.) Dr. B. J. Leonard, Dr. A. S. McFarlane, Dr. John Fahey (Bethesda): Myelomatosis.
FACULTY OF RADIOLOGISTS
4.30 P.M. (University College Hospital Medical School, W.C.1.) Prof. M. L. Rosenheim, Dr. C. J. Hodson: Radiology in Hypertension of Renal Origin.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
3.30 P.M. Mr. A. S. Walker: Management of Deaf Children.
INSTITUTE OF NEUROLOGY, The National Hospital, Queen Square, W.C.1
4.45 P.M. Dr. R. T. C. Pratt: Genetics.

Saturday, 17th

FACULTY OF RADIOLOGISTS
10 A.M. (Royal College of Surgeons, Lincoln's Inn Fields, W.C.2, with the R.S.M. *Section of Radiology.*) Dr. Irvan Yentis: Myelomatosis.

Copies of a memorandum on the *Rehabilitation of the Sick and Injured*, prepared for the Ministry of Health and the Central Health Services Council by the Standing Medical Advisory Committee, are being sent to all general practitioners in the National Health Service. It sets out the principles underlying modern methods of rehabilitation, which aim at securing the maximum recovery of health and practical efficiency after illness or injury; indicates the essential contribution which the general practitioner can make to this end; and describes some of the resources and facilities which are available.